

Zwitterionic polymers in biofouling and inorganic fouling mechanisms

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2.1 Introduction

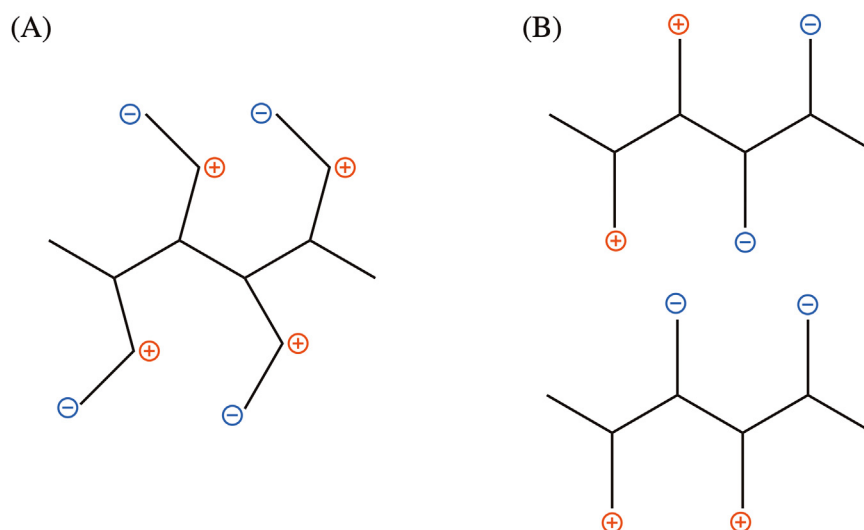
Zwitterionic (ZI) polymers, by definition, are characterized by the presence of equal numbers of anionic and cationic groups distributed along their polymeric chains with a net neutral charge (Mi & Jiang, 2014). First discovered in the 1950s by chemists who were trying to replicate the natural occurrence of zwitterions (i.e., naturally found in peptides and proteins) but in a laboratory setting, ZI polymers have just recently started being used as an alternative to the widely popular poly(ethylene glycol) (PEG) polymers especially in antifouling applications (Blackman et al., 2019; Li et al., 2020; Mi & Jiang, 2014). On the basis of the arrangement of these charged groups and chemical structures, ZI polymers can be categorized into two different groups: polybetaine polymers and polyampholyte polymers (Li et al., 2020). Polybetaine polymers have both anionic and cationic groups on the same monomer; polyampholyte polymers have them on different monomer units, as seen in Fig. 2.1 (Li et al., 2020; Zheng et al., 2017). Generally, ZI polymers are synthesized either by polymerization of manufactured ZI monomers or through postpolymerizations modifications (Blackman et al., 2019). Different polymerization techniques can be employed to produce ZI polymers, including but not limited to free radical polymerization, ionic polymerization, or ring-opening metathesis polymerization (Blackman et al., 2019; Laschewsky, 2014).

ZI polymers of the polybetaine type can be further categorized on the basis of the differences in anionic and cationic moieties. Common cations used in these polymers include quaternized ammonium, phosphonium, imidazolium,

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**FIGURE 2.1**

Schematic representation of both types of ZI polymers. (A) Polybetaine. (B) Polyampholyte.

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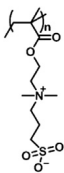
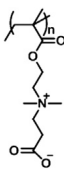
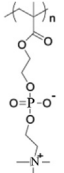
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and pyridinium. As for the anionic moiety, this could be sulfonate, which can be found in sulfobetaine-based polymers (SB), or carboxylate in carboxybetaine-based polymers (CB), or phosphonate in phosphorylcholine-based polymers (PC) (Li et al., 2020; Mi & Jiang, 2014). Currently, most research focuses on SB, CB, and PC polymers, which are associated with 2-(methacryloyloxy) ethyl 3-sulfopropyl dimethyl ammonium (SBMA), 1-(methacryloyloxy) ethyl 1-carboxymethyl dimethyl ammonium (CBMA), and methacryloyloxyethyl phosphorylcholine (MPC), respectively (Shao & Jiang, 2014). These different ZI polymers exhibit diverse properties according to their chemical structures, self-association capabilities, differences in charge densities between cationic and anionic groups, hydration, and hydrophilicities (Table 2.1) (Bengani et al., 2015; Shao & Jiang, 2014; Shao et al., 2010; Zhao et al., 2018). An additional feature worth mentioning is the ability of SB-based polymers to form a bicontinuous network; this has been associated with its high self-assembly. Zhao et al. (2018) studied the properties of four different hydrogels that contained three commonly used betaine-like ZI monomers and found that the high self-assembly characteristic is involved in the swelling feature of the hydrogels. They determined that MPC hydrogels exhibited no physical association and thus swelled larger than SBMA hydrogels, which were restricted by the physical junctions caused by their superior self-association.

The most common type of polyampholytes is the amino acid-based ZI polymers (i.e., ZI peptides). Many designs of polyampholytes can be found, one

Table 2.1 A comparative table of betaine-like monomers showing their differences in structure, hydration capability, difference in charge density between their cationic and anionic functional groups, and self-association capability.

Monomer name	Full monomer name	Monomer chemical structure	Hydration capability	Difference of charge density between cationic and anionic groups	Self-association capability	References
Sulfobetaine	2-(methacryloyloxy) ethyl 3-sulfopropyl dimethyl ammonium (SBMA)		Lowest	Moderate	Highest	Shao & Jiang, 2014 ; Shao et al., 2010 ; Zhao et al., 2018
Carboxybetaine	(1-methacryloyloxy) ethyl 1-carboxymethyl dimethyl ammonium (CBMA)		Highest	Highest	Lowest	
Phosphorylcholine	2-methacryloyloxyethyl phosphorylcholine (MPC)		Moderate	Lowest	Moderate	

of which is by alternately polymerizing positively charged and negatively charged amino acids (i.e., CRERERE) (Ye et al., 2015). Apart from ZI peptides, polyampholytes can also be constructed by polymerizing polyanions and polycations (i.e., PAMPS-*b*-PMAPTAC and PMAA-*b*-PDMAEMA, respectively) (Jhon et al., 2012).

Because of this structural diversity in the choice of charged moieties, ZI polymers show functional versatility; hence they are useful in multiple antifouling applications, including water treatment, industrial, and biomedical fields, such as coating membranes for water treatment, industrial marine pipelines, and biosensors with ZI polymers to prevent biofilm formation (Yang et al., 2009; Zheng et al., 2017). This versatility has been attributed to their high hydrophilicity, which is due to ionic solvation with water molecules, which form a tough hydration layer around the polymer chains by retaining water (Li et al., 2020; Zheng et al., 2017). This hydrophilic surface of ZI polymers makes them strong candidates for antifouling applications, including mechanisms that prevent biofouling, organic fouling, and inorganic fouling (Fig. 2.2) (Schönemann et al., 2019).

Because of the recent popularity of ZI polymers in antifouling applications, this chapter is organized into four main sections that thoroughly discuss ZI

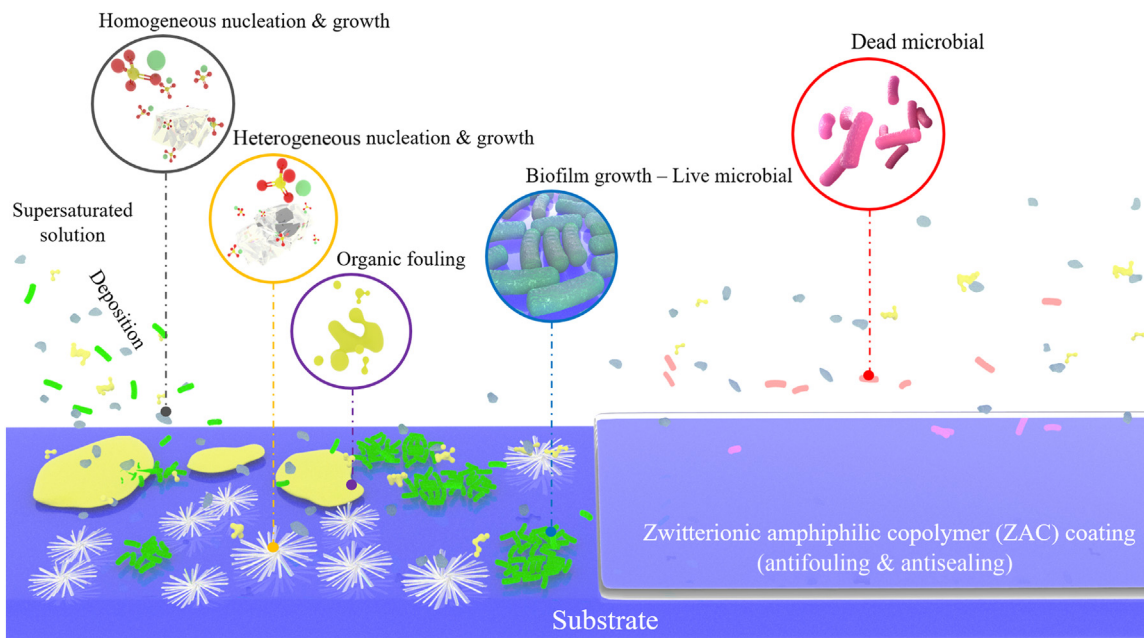


FIGURE 2.2

Schematic overview of organic fouling, biofouling, and mineral scaling on polymer surfaces.

membrane fabrication, ZI polymers, and their interactions with molecules and structures involved in the antifouling mechanisms, namely, inorganic fouling, organic fouling, and biofouling.

2.2 Zwitterionic membrane fabrication and characterization

To improve the membrane antifouling performance, various ZI polymers have been used to modify membranes through grafting (grafting-from or grafting-onto) and in situ modification processes (Li et al., 2020; Venault & Chang, 2018). Among them, grafting processes can functionalize the membrane through the covalent bond between the surface and the ZI polymer. In addition, the differences between graft-from and graft-onto strategies depend on how the synthesis of the ZI polymer occurs.

Grafting-onto refers to the process by which an already synthesized ZI polymer gets anchored onto the membrane surface via chemical bonding or physical interactions; grafting-from is the process by which the ZI polymer gets synthesized on top of the membrane. Regardless of the type of grafting process, the quality of the grafting is determined by both the material chemistry and the grafting coverage. In the case of grafting-onto coating processes, a relatively weaker interaction between the membrane surface and the ZI polymer can occur than with grafting-from. For instance, physical adsorption interactions, including hydrophobic interaction and electrostatic interaction, have been mentioned in previous studies of grafting-onto (Bengani-Lutz et al., 2017; Bengani et al., 2015).

The lack of requirement for membrane surface activation before coating allows the grafting-onto processes to have a lower cost and easier applicability in contrast to grafting-from. In the case of membranes prepared by in situ modification processes in bulk solution, the fabrication technique consists of using the main polymer for the membrane support layer and the antifouling ZI copolymer for the active layer. Typically, in this case the solvent is first blended and then used to form the membrane by exposing the casting solution to a nonsolvent (Venault & Chang, 2018). The major advantages of this method are that the ZI-modified membranes, including both the bulk membrane and membrane surface, can be fabricated in one step without any functionalization procedures before or after coating. Next, we will discuss them one by one in detail.

2.2.1 Grafting processes for membrane modification

2.2.1.1 Grafting-from process

In the grafting-from process, the initiator is first anchored on the membrane surface, and then a polymerization of monomers in solution occurs as

illustrated in Fig. 2.3 (Liu et al., 2017; Wang et al., 2015; Wang et al., 2016). This process can usually provide high polymer grafting density and stability. This grafting method used for membrane surface modification mainly includes surface-initiated (SI) atom transfer radical polymerization (ATRP), photo-induced polymerization, and plasma-induced polymerization (Birkner & Ulbricht, 2015; Chen et al., 2012; Ginic-Markovic et al., 2015; Guo et al., 2019; Jaramillo et al., 2021; Liu et al., 2017; Yang et al., 2018; Zhang et al., 2017). Among them, SI-ATRP has been the most frequently used method to modify membrane surfaces, owing to its wide applicability for various ZI monomers with different types of functional groups. For example, poly-SBMA brushes were grafted onto commercial polyamide thin-film composite (TFC) reverse osmosis/forward osmosis (RO/FO) membranes (Ginic-Markovic et al., 2015; Ma et al., 2019; Venault & Chang, 2018; Zhang et al., 2017). The dopamine-based initiator is first used to enrich the amine groups on the

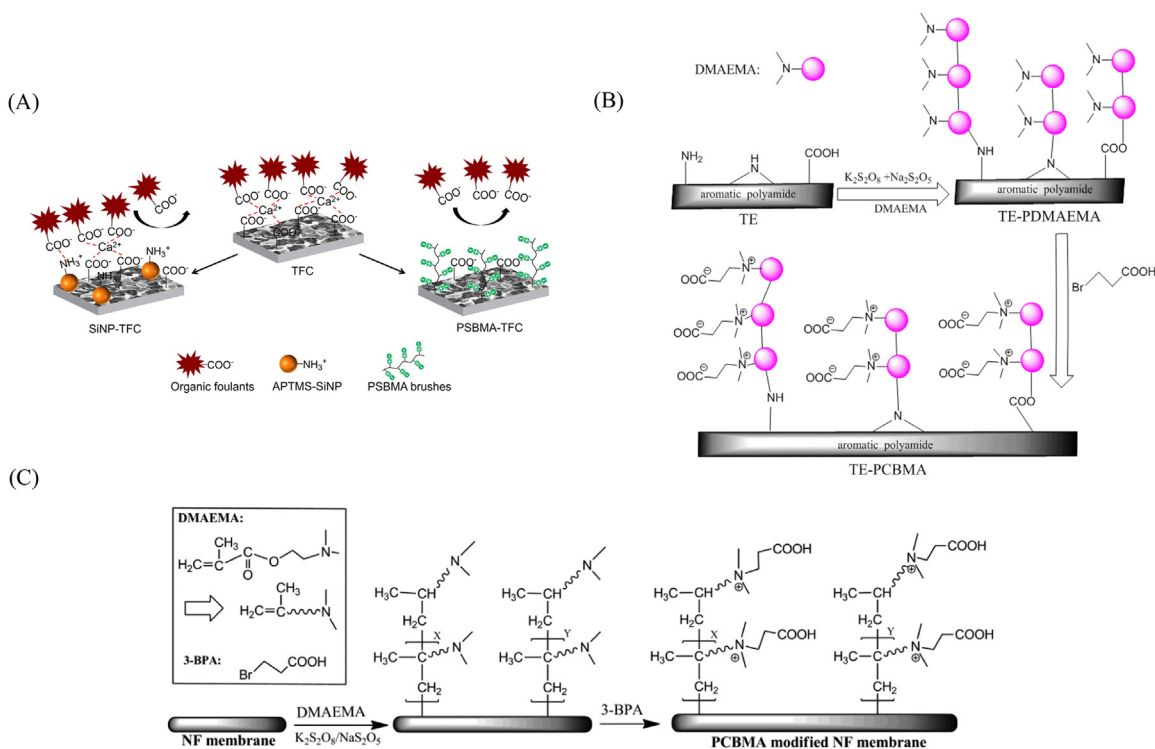


FIGURE 2.3

Schematic of modified membranes grafted by ZI polymers. (A) Schematic of surface modified with SiNP-modified thin-film composite (TFC) membranes (SiNP-TFC, pathway toward left) and ZI polymer PSBMA-modified TFC membranes (PSBMA-TFC, pathway toward right) (Liu et al., 2017). (B) Schematic of the membrane modified with PDMAEMA and then PCBMA (Wang et al., 2015). (C) Schematic diagram of DMAEMA, 3-BPA, and modification process on the surface of the NF membranes (Wang et al., 2016).

membrane surface. Then the surface amine groups react with the ATRP initiator, 2-bromoisobutyryl bromide, followed by surface-initiated polymerization of SBMA from the surface, using activators regenerated by electron transfer ATRP.

Yang et al. (2018) modified the polyamide RO membrane surface with a ZI polymer via SI-ATRP. Unlike the prior studies that we mentioned, the RO membrane surfaces in their studies were aminated with 3-aminopropyltrimethoxysilane treatment to immobilize the ATRP initiator (BIBB), and the ZI polymer poly[(2-methacryloyloxy)ethyl]dimethyl[3-sulfo-propyl]ammonium hydroxide was then grafted onto the surface of BIBB-immobilized membranes through ATRP.

After the grafting processes, those studies confirmed the successful modification with ZI polymer through both attenuated total reflectance Fourier transform infrared spectroscopy and X-ray photoelectron spectroscopy (XPS), and other surface characterizations (i.e., surface hydrophilicity, surface roughness, and surface charge). Meanwhile, the antifouling performance of modified TFC membranes was closely related to the chain length, the conformation of the polymer brush. During ATRP processes, properly controlling the polymerization time or the ratio of the initiator and monomer could tune the architecture of the polymeric surface coverage, thereby optimizing the membrane properties. For instance, it was revealed that the water permeability and salt rejection of ZI-modified RO/FO membrane after ATRP treatment was slightly reduced or unchanged in comparison to the control bare membrane. However, careful optimization of the PSBMA layer thickness via controlling both initiation and the subsequent polymerization time was able to improve the membrane permeability, thus maintaining the membrane transport properties (Ginic-Markovic et al., 2015; Jaramillo et al., 2021; Liu et al., 2017; Ma et al., 2019; Yang et al., 2018).

Besides ATRP, photo-induced and plasma-induced polymerization could also offer a simple synthesis pathway for surface modification. Stimuli-responsive ultrafiltration (UF) membranes were synthesized via photo-initiated grafting from of the ZI monomers sulfobetaine methacrylate, and CBMA onto polyether-sulfone (PES) UF membranes. The synthesis conditions in terms of UV irradiation time and UV intensity were varied in order to obtain the modified membranes, which presented desired stimuli-response behavior comparable to that of unmodified PES UF membranes; and the ZI-modified membrane permeability can change with variation of salt concentration (Birkner & Ullbricht, 2015).

Han et al. (2019) tried to graft ZI sulfobetaine methacrylate (SBMA) polymers onto hydrophobic polyvinylidene fluoride (PVDF) membrane for membrane distillation, using plasma-induced surface polymerization. The characterization results showed that the modified membranes had enhanced hydrophilicity and

slightly higher fluxes relative to the pristine membranes. [Chen et al. \(2012\)](#) tried to coat the polypropylene (PP) fibrous membranes with poly(sulfobetaine methacrylate) (pSBMA) via plasma-induced surface polymerization. The plasma treatment was believed to generate free radicals, which could initiate the cross-linking reactions. The grafting coverage of ZI polymer on the membrane surface could be controlled by using a low-pressure or atmospheric plasma treatment. In addition, pSBMA was immobilized on the lumen surface of the PVDF hollow fiber membrane by an ozone activation treatment, and the grafting density and chain length of the polymer were systematically optimized by the operating parameters ([Tang et al., 2017](#)).

Compared to surface grafting via ATRP, plasma-induced surface polymerization has a high grafting yield and short modification time. Also, photo-induced and plasma-induced treatments are easy to do and suitable for biomedical membrane modifications, which require dry and clean operating conditions. This is because the initiator and activator used in ATRP are toxic, and the reaction should be done under wetting conditions.

2.2.1.2 Grafting-onto process

The grafting-onto approach is another important method for surface modification. As we mentioned previously, the grafting-onto method is used when the ZI copolymer is first synthesized before being used for the membrane surface modification. Therefore this approach can achieve better control of the quality of the grafting process because the copolymer can be well characterized before grafting. Based on the literature, physical adsorption, including hydrophobic interaction and electrostatic interaction, has been widely employed in membrane surface modifications. In a study by [Wang et al. \(2018\)](#), the positively charged ZI copolymers were synthesized by using SBMA and [2-(methacryloyloxy) ethyl] trimethylammonium chloride monomers with a radical polymerization method, and they were then dip coated on the negatively charged membrane made by poly(vinyl chloride-*co*-acrylonitrile-*co*-sodium 4-styrenesulfonate) via simple electrostatic adsorption. In addition, the hydrophobic interactions between the hydrophobic membrane substrate and the ZI copolymer with a strong hydrophobic group were employed to modify the membrane.

[Venault et al. \(2014\)](#) tried to synthesize the diblock copolymer pSBMA and poly(propylene oxide), which can interact with any hydrophobic membrane materials, and they grafted the polymer onto the surface of PVDF membrane via a dip-coating process. After coating, the membrane surface composition, hydrophilicity, and charge were characterized by using XPS, a contact angle goniometer, and an electrokinetic analyzer, respectively, all of which confirmed the successful modification of the membrane with ZI. [Chou et al. \(2018\)](#) introduced the in situ self-assembling coating method, which consists

of synthesizing and simultaneously coating a ZI copolymer onto the hydrophobic surface. Under optimized conditions of concentration, molar ratio, and reaction time, the ZI copolymer composed of hydrophobic styrene and SBMA was coated on different hydrophobic surfaces made with varied materials, including PP, poly(dimethylsiloxane), and poly(tetrafluoroethylene).

In a study by Bengani-Lutz et al., ZI amphiphilic copolymers, which consist of the hydrophobic trifluoroethyl methacrylate and hydrophilic SBMA, were coated onto the hydrophobic surface of PVDF UF membranes. The permeability of the ZI-modified membrane was reduced in comparison to that of the uncoated PVDF membrane but comparable to or even higher than that of a commercial PES membrane which presented a size cut-off similar to that of the fabricated ZI membrane. They demonstrated that the thickness of the selective layer can be reduced by optimizing the membrane coating to achieve even higher permeance (Bengani et al., 2015; Bengani-Lutz et al., 2017). A scanning electron microscopy (SEM) image shows how these ZI copolymers are coated onto these membranes (Fig. 2.4) (Bengani et al., 2015).

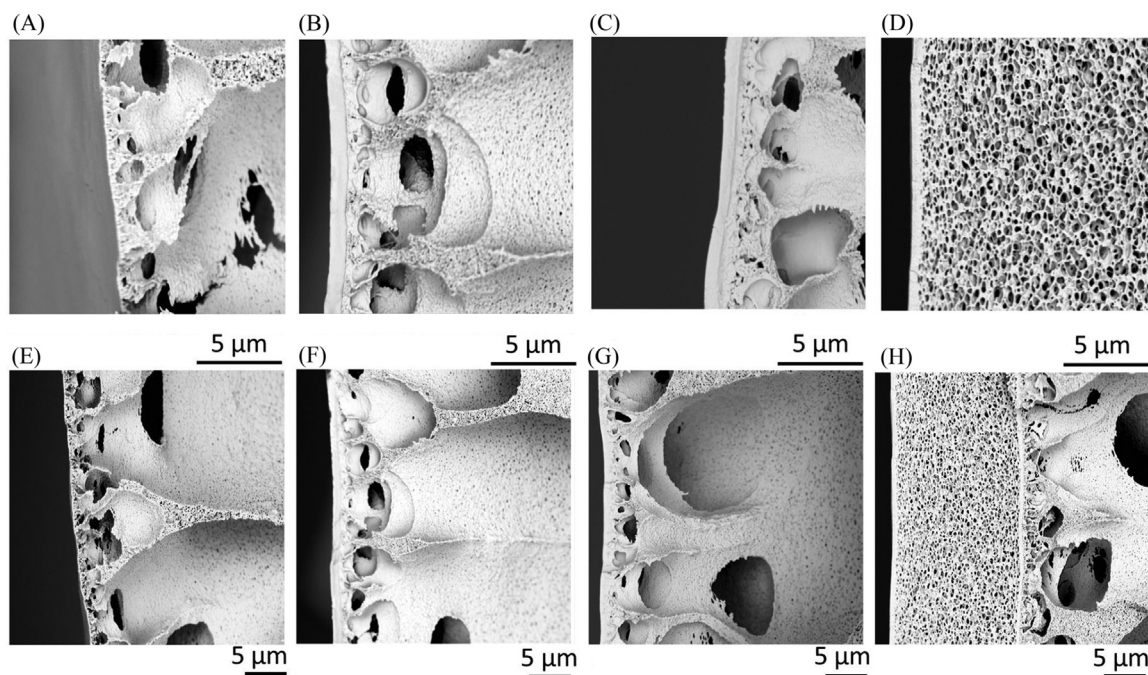


FIGURE 2.4

Cross-sectional SEM images of uncoated support membrane and thin-film composite (TFC) membranes with PTFEMA-r-SBMA selective layers with varying SBMA contents. (A, E) Uncoated support membrane. (B, C, D, F, G, H) TFC membranes made by coating with (B, F) P50 (50% SBMA), (C, G) P40 (40% SBMA), and (D, H) P30 (30% SBMA). (Bengani et al., 2015).

Compared to the grafting-from strategy, grafting-onto methods can make the ZI membrane synthesis more convenient and efficient, since there is no need for surface activation. However, it will cause a thicker coating compared to the grafting-from method. Therefore the permeability of ZI-modified membrane may be reduced dramatically compared to the unmodified membrane. This method is usually used for UF membranes, which have larger pore sizes. Similar to controlling the thickness of ZI brush in the ATRP process to achieve a higher permeance, optimization of the coating conditions to reduce the coating thickness is also needed in the grafting-onto process.

2.2.2 Membrane modification by in situ modification

During ZI membrane synthesis by in situ modification method, the hydrophobic polymer, the ZI copolymer consisting of hydrophilic and hydrophobic parts, and the solvent are first blended, and then the mixture solution is exposed to a nonsolvent (i.e., water). In that case, the hydrophilic groups in the ZI copolymer will draw the water to the polymer-water interface, whereas the hydrophobic groups will anchor together with the hydrophobic polymer to form the membrane support layer. The whole process is called nonsolvent-induced phase inversion (NIPS), which can incorporate the amphiphilic ZI copolymer segregates on both top surfaces and internal pore walls of the membrane without any added manufacturing steps. This manufacturing technique, which relies on phase separation of the ZI polymer, has been widely used to improve the fouling resistance of UF membranes (Kaner et al., 2017a; Qian et al., 2021; Zhao & He, 2015).

In a study by Kaner et al. (2017b), ZI-modified UF membranes were fabricated by blending the synthesized ZI copolymers (i.e., PMMA-*r*-SBMA and PMMA-*r*-SB2VP) with hydrophobic polymer PVDF by NIPS. Vapor-induced phase separation (VIPS) as another kind of in situ modification has been reported by Dizon et al. (Dizon et al., 2021; Dizon & Venault, 2018). Unlike NIPS, the casting solution during VIPS is exposed to atmospheric humidity instead of water. Low-fouling bicontinuous membranes of PVDF with ZI copolymer can be fabricated by VIPS from a casting solution of blending PVDF and triple copolymer poly(styrene-*co*-ethylene glycol methacrylate-*co*-SBMA) (Dizon & Venault, 2018).

In another study, to fabricate ZI copolymer-modified membranes, poly(methyl methacrylate-*co*-ethylene glycol methacrylate-*co*-sulfobetaine methacrylate) (PMMA-*r*-PEGMA-*r*-PSBMA) was synthesized by using free radical polymerization and blended with PVDF to form ZI membranes in one step via VIPS. Compared to their above study, changing polystyrene to PMMA as the anchoring block to synthesize the ZI copolymer could facilitate the

formation of ZI membranes by in situ modification (Dizon et al., 2021). After forming the membranes by VIPS, full characterizations (i.e., SEM, AFM, FT-IR, and WCA) were conducted to confirm the existence of ZI copolymer on the membrane. In those studies, ZI membranes fabricated by in situ modification usually have a good permeance due to large membrane porosity and pore size. This makes the method suitable for microfiltration and ultrafiltration membrane fabrication. Compared to the classic grafting method, the advantages of using in situ modification are the simplicity of the preparation steps and preservation of the surface porous structure without compromising the membrane transport properties.

To summarize, ZI-coated TFC membranes can be fabricated through surface-initiated grafting-from, grafting-onto, and in situ modification. Different techniques have different merits and limitations. First, the grafting-from process with ATRP needs stringent experimental conditions; however, it can enable higher polymer densities than the grafting-to approach. Before coating with this method, an additional surface activation step can add to the cost of the membrane fabrication. Furthermore, the whole functionalization process easily leads to decreased flux as pores are partially filled with the attached functional groups. Second, for the “grafting-onto” coating processes, this approach is advantageous in terms of ease of operation, mild modification conditions, and simple posttreatment method after membrane fabrication. However, the method is only applied to certain specific interactions including hydrophobic and electrostatic interactions. Expect for the membrane surface, the in situ modification can even modify the surface properties of the internal pores, which cannot be done using most classical grafting methods. However, there are some concerns: for NIPS method, on one hand, it is not an easy process to control because the surface-modifier (hydrophilic or amphiphilic) does not mix well with polymer matrix (hydrophobic) and the solvent. On the other hand, most of the polymer material in NIPS process is used to fabricate the support layer, which has no functional purposes for the membrane permeability or sieve. Therefore the selection of the ZI membrane fabrication method by researchers should consider each specific application scenario and the goal they are seeking to achieve. For instance, the grafting-from method, that is, ATRP, are more suitable for RO/FO membrane modification, because they have relative smaller pore size and thin thickness ($\sim 0.1 \mu\text{m}$) of the active layer. Even though an extra coating layer is added to the RO/FO membrane surface, carefully controlling the architecture of the ZI brush can avoid compromising intrinsic membrane transport properties. While for grafting-onto and in situ modification strategies are more applied for microfiltration/ultrafiltration membrane, which has larger porosity and pore size. The former one can produce higher permeance and sieve capability through optimization of the thickness of ZI coatings. For in situ

modification, it can fabricate ZI membranes with good surface porous structure in a simple procedure, which can guarantee higher permeability. Since maintaining transport properties similar to those of the unmodified membrane is a prerequisite for antifouling studies of ZI membranes, in addition to ZI membrane synthesis, there are a lot of studies focused on understanding the antifouling performance of ZI coatings with different foulants, such as antiscaling, antiorganic fouling, and antibiofouling, as described in the next sections.

2.3 Zwitterionic polymers and inorganic fouling

Inorganic fouling is usually caused by the precipitation or crystallization of soluble salts, especially when their concentration in feed water reaches the solubility limit with respect to the inorganic salts (Ansari et al., 2021; Liu et al., 2019; Qi et al., 2020). It is known that natural waters, including brackish water and seawater, often contain various types of inorganic mineral ions (e.g., calcium, sulfate, carbonate, and phosphate), which can produce insoluble minerals (e.g., gypsum, calcite, and calcium phosphate) and generate inorganic fouling. Moreover, mineral scales are usually formed through directly surface-induced heterogeneous precipitation or homogeneous precipitation in the bulk solution (Antony et al., 2011). Surface-induced heterogeneous precipitation normally occurs on surfaces that can serve as nucleation sites when the substrate can lower the nucleation energy barrier. While homogenous precipitation often take place especially when the nuclei size in bulk solutions exceeds the critical size that is determined by the interfacial energy between the nuclei and the liquid (De Yoreo, 2003).

Inorganic fouling is a major concern in the fields of membrane desalination, heating systems, and pipeline transportation (Sojoudi et al., 2019; Tong et al., 2019; Zhao et al., 2005). To achieve scaling mitigation in membrane desalination, only the hydrophilic SB-based ZI polymer brushes have been shown to improve the membrane antiscaling performance (Jaramillo et al., 2021). The other ZI polymers either have not been investigated or have been poorly investigated. However, because of the vast library of ZI materials and their diverse associated characteristics, more research should be done to better determine and understand the potential uses and applications of ZI polymers to prevent inorganic fouling.

As was mentioned previously, ZI materials have strong self-hydration capabilities due to the solvation of both positively and negatively charged functional groups. These functional groups also make the ZI materials produce antipolyelectrolyte features, especially for polyzwitterionic polymers. For example, their cationic and anionic moieties can bind counterions in the salt

solution, which gives ZI polymers different conformations and higher solubility in salt solutions compared to pure water (Shao et al., 2010). Therefore the salt response properties of ZI materials may lead to different interactions between ZI materials and inorganic compounds, including pure salt ions. A good understanding of the interactions of ZI polymers with inorganic compounds can help in determining the scaling mechanisms on ZI-modified membrane surfaces. Next, we will discuss the ionic interactions of ZI with salts and the mineralization mechanisms in the presence of ZI.

2.3.1 Zwitterionic polymers and ionic interactions

It has been widely reported that the conformation of ZI brushes is affected by the ionic strength and types of ions present in the solution. Typically, ions in an aqueous solution can be classified as kosmotropic or chaotropic, which refer, respectively, to their ability to stabilize or destabilize water-water interactions. In terms of hydration strength of these ions, that is, their affinity to water, it has the following order: $K^+ > Na^+ > Ca^{2+} > Mg^{2+}$. Leng et al. studied the interactions between different types of cations (i.e., Na^+ , K^+ , Ca^{2+} , and Mg^{2+}) and ZI polymers and found that ZI polymer brushes have stronger affinity to divalent cations (i.e., Ca^{2+} and Mg^{2+}) than monovalent cations (i.e., Na^+ and K^+), owing to the stronger electrostatic attraction of divalent cations compared to monovalent cations. Hence the addition of divalent cations can cause the hydration loss of ZI surfaces and reduce their fouling resistance in comparison to monovalent cations (Leng et al., 2014). Furthermore, the monovalent cation association at lower salt concentration does not disrupt the proper ordering of water at the interface between water and the ZI polymer. Therefore the surface hydration of ZI polymers is not affected by monovalent ion adsorption, which maintains the nonfouling behavior of the ZI polymer in a high-salt environment.

Wang et al. (2013) investigated the effects of different anions (i.e., SCN^- , ClO_4^- , ClO_3^- , Br^- , Cl^- , and SO_4^{2-}) on the conformation of pSBMA brushes in various salt solutions with different ionic strengths. They demonstrated that those anions have different capabilities to weaken the interchain and intrachain associations of the ZI polymers and followed a direct and reverse Hofmeister series under low and high ionic strength conditions. It should be noted that the addition of sulfate anion could dehydrate the grafted chains in higher ionic strength conditions, which presents an opposite behavior with the other anions. This was because the most kosmotropic divalent anions (i.e., SO_4^{2-}) could compete for water molecules with the polymer chain. Hence the researchers concluded that the difference in the extent of hydration of the graft chain that was induced by varied types of anions could cause anion-specific conformation behavior of ZI polymer brushes (Wang et al. 2013, 2014).

In another study by [Zhang et al. \(2016\)](#), the effects of different salts on the surface properties of pMPC brushes were studied by using ellipsometry, quartz crystal microbalance with dissipation (Q-CMD) measurements, and friction force microscopy. They found that the hydration capabilities and conformation structures of pMPC brushes were independent of the addition of ions under all study conditions, owing to the excellent hydration capability of phosphonate functional groups in the ZI polymer. However, both cation and anion adsorption on PC functional groups could affect the intramolecular-intermolecular association and stiffness of the pMPC brushes, thus changing the lubrication performance of pMPC brushes. Moreover, the varied binding affinity of ions to PC groups determined the ion-specific lubrication performance of the pMPC brush layer. For example, the addition of kosmotropic sulfate ions could easily disrupt the hydrogen bonding between water and the phosphonate function groups, thus worsening the lubrication performance of the pMPC brushes ([Zhang et al., 2016](#)).

In summary, once a ZI polymer has been grafted onto a substrate, it can provide a superhydrophilic layer on the surface ([Li et al., 2020](#); [Zheng et al., 2017](#)). This is because the cationic and anionic functional groups of ZI materials can attract a large number of water molecules around the polymer chains through charge-dipole interactions and hydrogen bonding ([Shao et al., 2014](#); [Shao and Jiang, 2014](#)). From those studies, it was determined that inorganic ions can influence the properties of ZI polymer brushes by affecting the ordering of water molecules at the interface between water and polymer. For example, the kosmotropic cations can lead to more hydration of the polymer compared to chaotropic cations, while the enhancement of the anion to the hydration of polymer chains depends on the ionic strength and the types of salt. Furthermore, chaotropic anions can cause a more hydrated polymer chain in contrast to kosmotropic ones under lower ionic strength conditions. On the other hand, the above-mentioned results are reversed under higher ionic strength conditions. Therefore in real-life applications, ZI polymer brushes with controllable surface properties are ideal candidates for tailor-made stimuli-responsive surfaces, such as biocompatible substrates and self-lubricating surfaces. These fundamental findings regarding the ionic interactions with ZI materials can serve as a guide for the development of such functional surfaces.

2.3.2 Mineral scaling on ZI-modified membranes

The scaling resistance of ZI polymers have been explored in many applications related to membrane desalination. In the field of water treatment the use of an antiscalant might delay the onset of precipitation but have minimal impact on the nucleation or growth of mineral scales on membranes.

In general, thin-film antiscalant coatings for membrane desalination treatment are highly efficient alternatives to antiscalants because the coatings can affect the energy barrier of mineral nucleation, leading to attenuation of mineral nucleation and deposition (Sojoudi et al., 2019). Therefore superhydrophilic ZI materials are used to modify different water separation membranes to improve their antifouling and antiscaling performances.

In the work of Jaramillo et al. (2021), ZI polymers, such as pSBMA polymer brushes, were used to functionalize the commercial RO membrane through ATRP. They observed that ZI polymer coatings delayed bulk and surface-induced gypsum crystallization on the membrane. The antiscaling mechanisms were revealed to be due to two factors. First, the authors mentioned that the surface energy of ZI polymer-modified membranes was higher than that of the control membranes, owing to their relatively superior surface wetting capabilities. Second, it was postulated that the polymer brush-like morphology of pSBMA polymers sterically hindered the attachment of gypsum nuclei. Even though these authors investigated the role of ZI materials in the field of membrane antiscaling, there are still several research questions that need to be addressed. First, the ATRP modification procedure can graft the hydrophilic surface coating onto the commercial membrane, but it can also reduce its permeability. Alternative grafting methods should be investigated to gain a better understanding of the antiscaling behavior of ZI coatings without lowering the membrane's permeability. Furthermore, the authors analyzed the underlying mechanisms of ZI against scaling only from the perspective of surface thermodynamics; however, the interaction between scale-forming ions, including calcium and sulfate ions and ZI polymer-modified membranes, should be taken into consideration. To summarize, numerous studies have investigated the antifouling properties of ZI materials, but the control mechanisms of ZI in mineral scaling are far from well understood. Overall, these studies imply that superhydrophilic ZI materials could be promising for the development of scaling-resistant desalination membranes.

2.4 Zwitterionic polymers and organic fouling

Organic fouling is the deposition of unwanted organic materials, such as proteins, lipids, and carbohydrates, onto a surface. These foulants can adsorb and accumulate on surfaces, leading to major issues. In the field of water treatment, these issues include lowering the performance of the membrane filtration or even degrading the materials that are used in marine environments such as ship hulls and ropes. In this section the research presented will be applied to membrane technologies with the most studied organic foulant proteins. Proteins are polypeptides made of amino acids, which

contain an amino group, a carboxyl group, and a side chain. These side chains can be either polar, nonpolar, or charged, and they determine the final structure and conformation of these polypeptides.

Among the proteins that are commonly investigated for organic fouling mechanisms, lysozyme and bovine serum albumin (BSA) are the two most frequently used. Lysozyme is a positively charged protein, and BSA is known to be negatively charged. Protein adsorption investigations have led to further understanding of biofouling and how cells initiate biofilm formation on a surface, which will be further discussed in later sections. A solution to organic fouling could be the use of ZI polymers, which, when coated onto a surface, are very resistant to organic foulants by preventing their adsorption. In this section we discuss the mechanism and conditions that allow ZI polymers to resist organic fouling.

2.4.1 The Mechanisms of zwitterionic polymers' resistance to organic fouling

In this section we discuss the known mechanisms of organic fouling inhibition on surfaces coated by ZI polymers. When surfaces or membranes are modified with ZI polymers, they tend to do well at resisting nonspecific protein adsorption (Zhang et al., 2020). In the case of membranes, ZI polymers were found to retain antifouling properties against proteins and other organic foulants as well as recover flux after washing off these foulants. So far, three main properties of ZI involved in antifouling mechanisms have been identified: surface hydrophilicity, charge, and the orientation of free water molecules onto the ZI polymer.

ZI polymer-coated surfaces have been shown to change the hydrophilicity of the surface. In the study by Li et al. (2017), silver nanoparticles (AgNP) were coated with pCBMA and then immobilized on a PVDF membrane. The AgNP-pCBMA coating increased the hydrophilicity of the PVDF membrane and prevented BSA fouling, as shown in Fig. 2.5 (Liu et al., 2017). In a study by Liu et al. (2017), silica nanoparticles (siNPs) and pSBMA were coated onto a polyamide TFC used for forward osmosis. Both siNPs and pSBMA increased the hydrophilicity of the membrane and presented a similar surface roughness; however instead of proteins, alginate, a polysaccharide, was used as the organic foulant model. The pSBMA was shown to have the highest permeance recovery. The chemical force microscopy demonstrated that the carboxyl groups of the alginate attached well onto the siNP surface, while the pSBMA surfaces were shielded from carboxyl interactions. Both of these studies demonstrate that the hydrophilicity of ZI polymers correlates well with their antifouling properties.

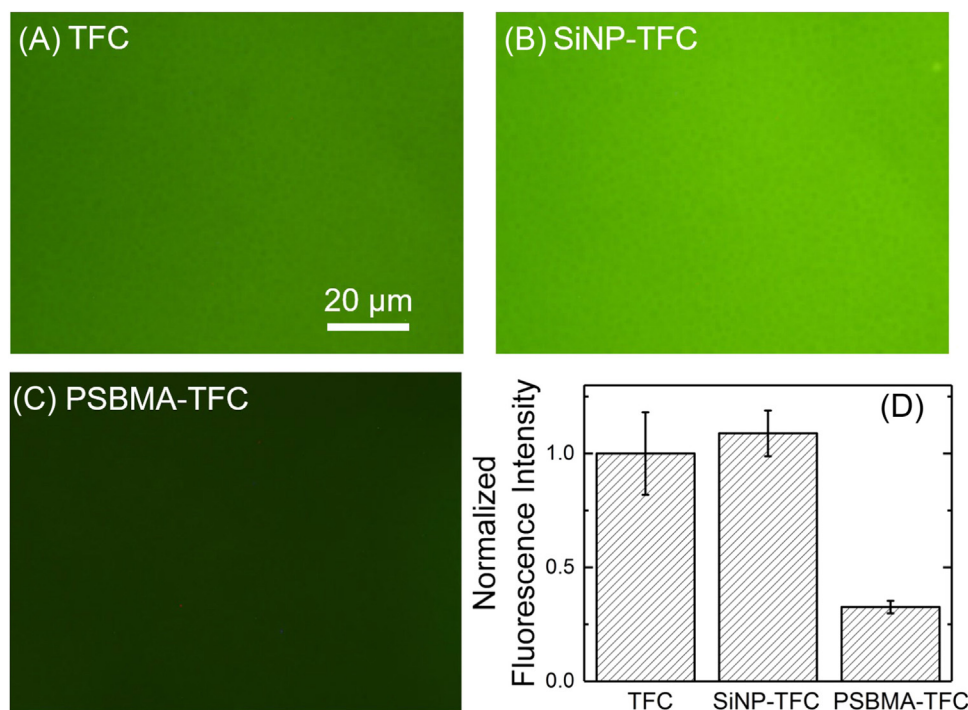
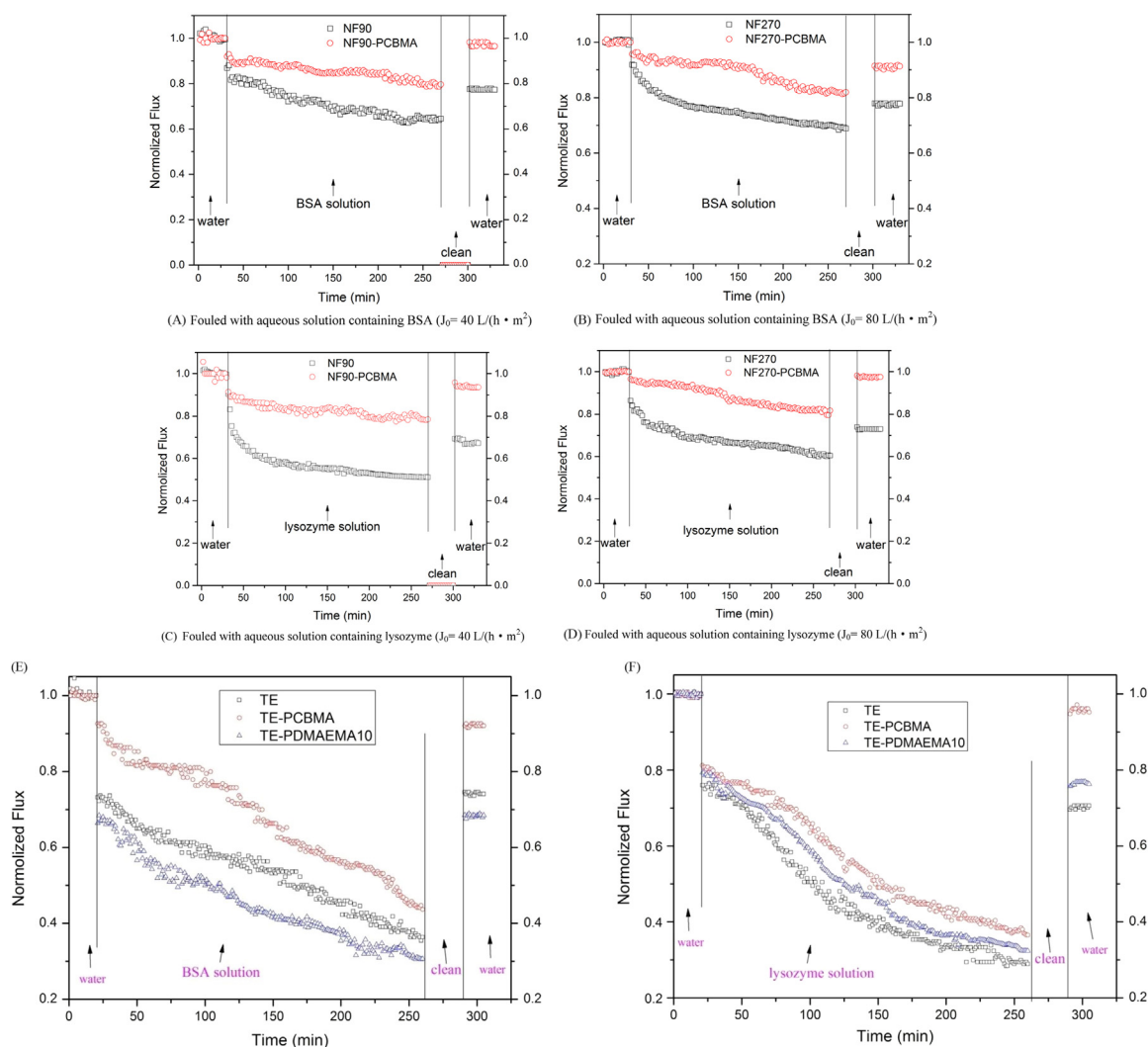


FIGURE 2.5

Epifluorescence microscopy of pristine and modified thin-film composite (TFC) membranes after fouling with fluorescein-labeled bovine serum albumin (BSA). (A) Pristine TFC, (B) SiNP-TFC, and (C) PSBMA-TFC membranes after exposure to a BSA solution. (D) Average fluorescence intensity normalized by the pristine TFC membrane (Liu et al., 2017).

ZI polymers have also been shown to change the charge of the coated surface. In a study done by Wang and collaborators (Wang et al., 2015), the research group modified the aromatic polyamide RO (TE) membrane by grafting the ZI pCBMA onto the surface. The unmodified membrane was shown to have a negative charge, while the modified pCBMA membrane had a neutral charge. Another membrane was modified with the precursor of pCBMA, poly-N,N'-dimethylaminoethyl methacrylate (PDMAEMA), which had a positively charged surface. All three modified surfaces were subjected to fouling using lysozyme and BSA, as demonstrated in Fig. 2.6 (Wang et al., 2016, 2015). The membrane that was modified with pCBMA showed the highest recovery of permeance after washing off the proteins when compared to the PDMAEMA and TE membranes. These results demonstrate that the charge of the surface contributes to the antifouling property of the ZI polymer and that neutral charges generated by ZI can improve antifoulant properties.

**FIGURE 2.6**

(A, B, C, D) Normalized permeation flux of nanofiltration (NF90 and NF270) and modified nanofiltration (NF90-PCBMA and NF270-PCBMA). (A, B) The membranes are fouled with BSA solution. (C, D) The membranes are fouled with lysozyme (Wang et al., 2016). (E, F) Normalized permeation flux of TE, TE-PDMAEMA10, and TE-PCBMA membranes fouled with a solution contain (E) 1000 mg L^{-1} BS and (F) 1000 mg L^{-1} lysozyme cleaned with water at 25°C , pH 6.8 (Wang et al., 2015).

Another possible contribution to the antifouling properties of ZI coatings could be the way in which free water molecules are arranged around the charged functional groups of the ZI polymers (Chen et al., 2008). A molecular dynamic stimulation of an immobilized artificial membrane surface with

PC groups was performed and demonstrated that the free water molecules would quickly surround charged functional groups of ZI and form an energy barrier, which reduced the attachment of biomolecules, such as proteins, to the surface (Ishihara et al., 2017). Ishihara et al. would later use ZI polymers containing PC, such as pMPC, to measure the hydration of the polymer by using scanning calorimetric analysis (Sakaki et al., 1999). It was revealed that polymers containing pMPC had a higher water fraction, which demonstrated that there was an interaction between water molecules and the ZI polymers, than the polar polymers such as poly(2-hydroxyethyl methacrylate) (pHEMA). They also demonstrated that polymers containing pMPC resisted better to the adsorption of BSA and bovine plasma fibrinogen than pHEMA (Sakaki et al., 1999). These results show a possible correlation between having a higher water fraction surrounding the polymer and the ability to resist protein adsorption. Han et al. (2018) demonstrated that the water orientation around the charged groups could change depending on the pH and salt concentration of the environment in which the ZI polymers are placed.

The research demonstrated that the ZI polymers increase the hydrophilicity and modify the charge of the surface. These changes could also affect interactions with water and determine the antifouling property of surfaces coated with ZI polymers. As was previously shown, the higher hydration of pMPC produced a more resistant protein-fouling property compared to the polar pHEMA molecule. This indicates that the free water molecules can form a barrier against fouling, as has been demonstrated in molecular dynamic studies (Sheng et al., 1995). pSBMA and pCBMA, which have different distal charges compared to pMPC, have also been shown to have this barrier created by water molecules, which could be a potential area of study to correlate the role of distal charges in ZI polymers with the orientation of free water molecules and the effectiveness of its antifouling property (Liu et al., 2017). Despite the natural effects of charge, hydrophilicity, and water orientation of ZI, environmental conditions could directly affect fouling as well, and this requires further research in real-life applications and settings.

2.4.2 The environmental conditions and organic foulants that influence zwitterionic polymers

In this section we discuss the environmental conditions that could affect the antifouling property of the ZI polymer as well as the effects of the size and charge of the organic foulants in the antifouling processes. Although the ZI polymer can change the surface's charge and hydrophilicity, the orientation of the free water molecules can be directly affected by the environmental

conditions and therefore affect the antifouling properties of the ZI polymers (Han et al., 2018; Leng et al., 2014). The main environmental conditions that will be discussed are the pH and the salt concentration.

The pH of the environment has been shown to influence the resistance of ZI polymers to organic fouling. In a study by Han et al. (2018), sum frequency generation (SFG) vibrational spectroscopy was used to study the orientations and interactions that water has on the surface of ZI polymers. In one study, pSBMA and pCBMA were coated onto silica prisms and put into water under various pH conditions. The two ZI polymers responded differently with the pH variations. pSBMA had a random orientation in water at pH 2, whereas the water surrounding pCBMA was shown to have a random orientation at pH 12. In a study by Leng et al. (2014), the ZI pCB acrylamide was modified with one (CBAA-1) and two (CBAA-2) carbon atoms between the charged functional groups. CBAA-1, CBAA-2, and SBMA were also coated on silica prisms and put into various pH conditions. At pH 5, CBAA-2 was shown to have a random water orientation, while pSBMA and CAA-1 had an ordered orientation. In a study by Kuo et al. (2011), pSBMA was copolymerized with acrylic acid and used to coat a tissue culture polystyrene 96-well plate surface. The experiments at pH 3 with fibrinogen and platelets, which are elements that are involved in blood clotting, showed the most resistance to adsorption. This study demonstrates that the pH influences the orientation of the free water molecules, which has a correlation with the ability to resist organic fouling. These studies, despite not being directly related to membrane investigation, have a direct implication in membranes that could potentially use these polymers in the treatment of different water chemistries with different pH values.

Salt concentration in solution could also influence the antifouling properties of ZI polymers. In a study by Han et al. (2018), pSBMA and pCBMA were put into a solution of 0.2 M NaCl, and the orientation of water and salt binding were measured through SFG spectroscopy. The pSBMA was immediately affected by the salt solution after its introduction, whereas the NaCl solution caused less disturbance of the water orientation in the pCBMA polymer. The authors explained that pCBMA has a stronger interaction with water molecules than pSBMA. Although, as was stated in the section on ionic interaction, Leng et al. (2014) demonstrated that ZI polymers have a higher affinity to divalent cations (Mg^{+2} and Ca^{+2}) than monovalent cations (Na^{+} and K^{+}) when there is a high concentration of salts, which could also explain this observed phenomenon by Han et al. (2018). In another study, Mi et al. (2012) investigated the interactions of Mg^{2+} and its role in mediating the interaction with polysaccharides and ZI polymers (pSBMA, pCBMA-2, and pCBAA-1). They demonstrated that divalent cations could bridge the adsorption of biomolecules onto the ZI polymer surface.

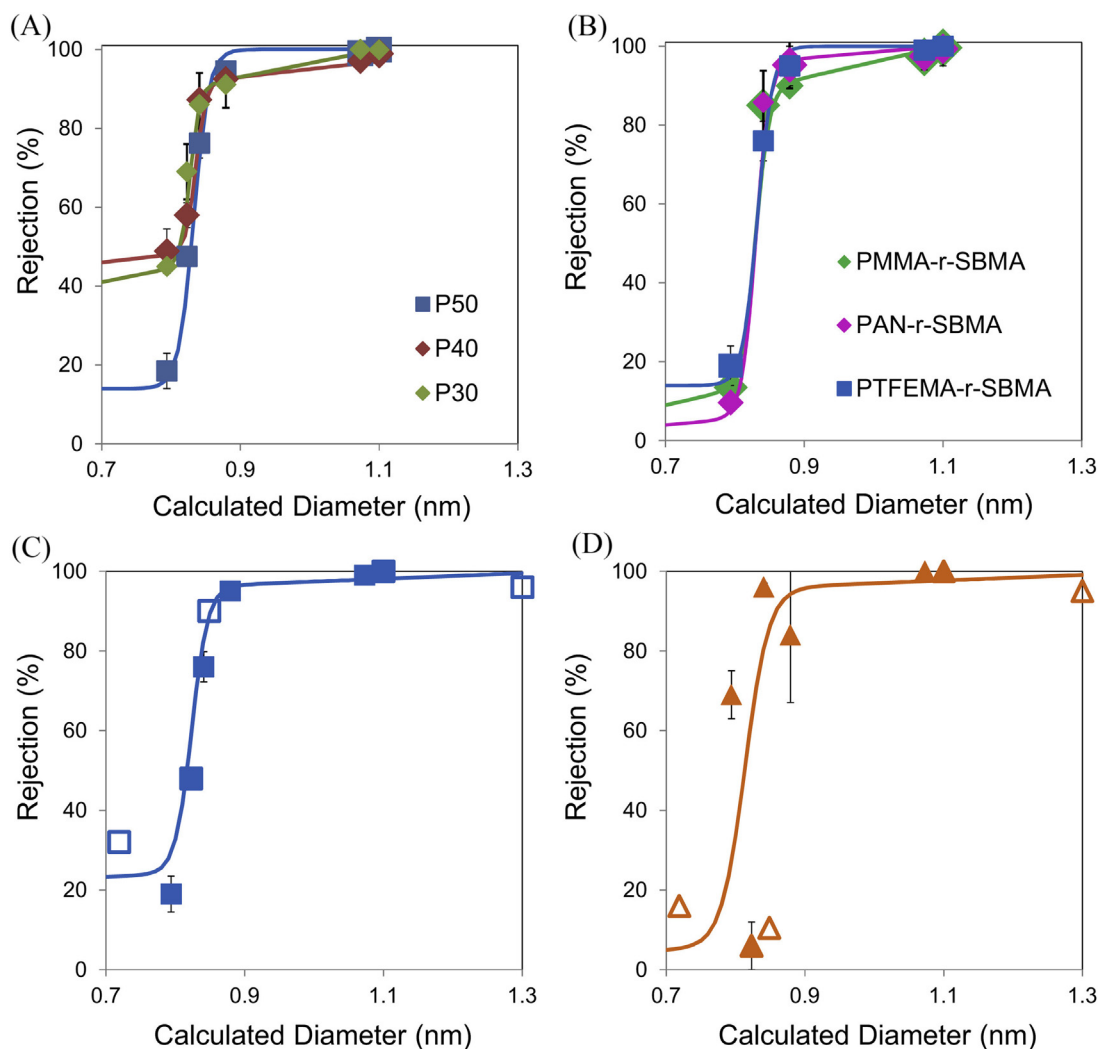
The size of organic foulants can also influence the antifouling resistance of ZI polymers. In a study by [Zhang et al. \(2020\)](#), RO membranes were coated with a ZI polymer quaternized 2,6-diaminopyridine (QDAP) to test its antifouling properties. The QDAP-modified membrane was fouled with a variety of organic foulants and proteins such as sodium dodecyl sulfonate, dodecyl trimethylammonium chloride (DTMA), lysozyme, and BSA. In each case, the presence of the coating improved the flux recovery; the lowest recovery was caused by the presence of DTMA, which is a small positively charged organic foulant ([Zhang et al., 2020](#)). The Q-CMD results suggested that the size of the molecule could affect the biomolecule adsorption to the surface because DTMA was shown to have a higher adsorption compared to larger molecules such as BSA and lysozyme ([Zhang et al., 2020](#)).

In another experiment, the ZI polymer pSBMA was copolymerized with polytrifluoroethyl methacrylate and coated onto poly(ether sulfone) 1000 molecular weight cut-off membranes, then tested to separate molecules ($<1500 \text{ g mol}^{-1}$), which were made of dyes and vitamins with different sizes and charges. Interestingly, these ZI copolymers were able to separate the molecules on the basis of their size with a cut-off of 1 nm, regardless of whether they were negatively or positively charged as shown in [Fig. 2.7](#) ([Bengani et al., 2015](#)). Through transmission electron microscopy, self-assembled nanochannels were demonstrated to form with the ZI copolymer, which led to the observed selectivity. The water flux with these ZI copolymers has also been shown to easily recover after a fouling test with BSA was performed ([Bengani et al., 2015](#)).

These studies showed that environmental factors and conditions can influence the interactions of organic molecules with ZI polymers. High concentrations of salts and highly acidic or basic conditions, depending on the functional groups of the ZI polymer, could affect their antifouling properties ([Han et al., 2018](#); [Leng et al., 2014](#)). These results indicate the importance of the water orientation in relation to the ZI polymer and the role of the water barrier in organic fouling as well as in biofouling resistance, which will be discussed in more detail in the next section.

2.5 Zwitterionic polymers and biofouling

Biofouling is a process through which biological molecules, prokaryotic and eukaryotic cells, nonspecifically adsorb to different types of membranes or surfaces such as biosensors, tissue scaffolds, food storage packages, implantable devices, surgical tools, and marine surfaces ([Erathodiyil et al., 2020](#); [Farkas et al., 2021](#); [Zhang et al., 2021](#)). In most cases, biofouling presents a challenge and should be prevented in a wide range of fields and

**FIGURE 2.7**

Thin-film composite (TFC) membranes modified with Zwitterionic (ZI) amphiphilic copolymers compared to commercial selective size membranes. (A) The rejection of anionic dye with TFC modified with PTFEMA-r-SBMA with various concentrations of SBMA: 50%, 40%, and 30%. (B) The rejection of anionic dye of TFC ZI amphiphilic copolymers with three different hydrophobic components: PTFEMA-r-SBMA (50), PMMA-r-SBMA, and PAN-r-SBMA. (C, D) Rejection of charged molecules (*solid symbols*) and neutral (*open symbols*) molecules. (C) P50-coated membrane. (D) Commercial PES 1 kDa membrane. (Bengani, et al., 2015).

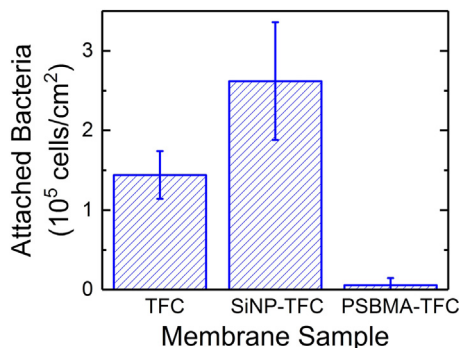
applications, including medicine, the marine industry, water treatment and filtration, and the food industry (Erathodiyil et al., 2020; Sadan et al., 2022).

In general, biofouling caused by prokaryotic and some unicellular eukaryotic organisms (i.e., algae) starts with the deposition of organic and inorganic

molecules on membranes or other surfaces through physical forces such as electrostatic interactions, van der Waals forces, and Brownian motion. At this stage, proteins, proteoglycans, and polysaccharides adhere to the surface, and adsorption of these cells is initiated. Over time, the cells start to adhere, secrete exopolysaccharide substances, and multiply to form a complexly arranged network that supports, stabilizes, and protects the surrounding cells. In the case of bacteria this newly formed structure is referred to as a biofilm (Almeida et al., 2007; Harding & Reynolds, 2014). Animal and human eukaryotic cell biofouling in complex systems, such as the human body, is more complicated. This biofouling process is initiated by the adsorption of serum proteins and ECM components, which trigger a handful of cellular pathways that initiate cell adhesion through adhesion receptors where integrins are predominantly involved, followed by proliferation, and maintenance of viability. Some of the pathways that are triggered throughout these processes include the focal adhesion and cytoskeleton remodelling pathways, which promote further cell adhesion and cellular spreading on surfaces (Yang et al., 2013).

Generally, microbial biofouling (and formation of biofilms) has a devastating outcome when it takes place on water filtration membranes. Bacterial fouling and biofilm formation have serious consequences when they happen on the surface of membranes. These significantly reduce the permeability and efficacy of these membranes. A direct consequence of these incidences is a drastic increase in operation and maintenance costs and a decrease in the endurance and lifespan of the membrane, leading to the need for a complete replacement of the membrane filter (Zhang et al., 2017). However, biofouling does not always have devastating outcomes. It can also be beneficial, especially when it takes place on the surface of medical implants and when the cells involved are those of the tissue surrounding the implant. Medical implants need to have a surface that resists biofouling by bacterial cells in order to prevent infection, but on the other hand, the surface needs to be biocompatible and boost adhesion of eukaryotic cells for enhanced recovery and function (Pham et al., 2016).

When cells have been put under suitable signals, they have been shown to be able to adhere and proliferate on ZI-coated surfaces. Owing to the outstanding antifouling or even enhanced biofouling properties of zwitterions, ZI polymers have been proposed to be used as coatings for antibiofouling purposes of membranes and water filtration units, as demonstrated in Fig. 2.8 (Liu et al., 2017). Consequently, in the next sections we will be reviewing the interactions of ZI polymers with prokaryotic and eukaryotic cells to lower or even enhance cell adhesion and their implications in the water filtration field and other fields that could also benefit from this feature.

**FIGURE 2.8**

The amount of live cells (*Escherichia coli*) attached to the surface of pristine and modified membranes (Liu et al., 2017).

2.5.1 Zwitterionic polymers and their interaction with prokaryotic cells

ZI polymers have been shown to significantly reduce biofouling by preventing the adhesion of microorganisms onto coated membranes and inhibiting the formation of biofilms (Yang et al., 2010; Zheng et al., 2017, 2021). This anti-biofouling feature of ZI has implications not only in marine environments as a replacement for the currently available solutions, such as coating marine surfaces with antifouling paints (i.e., tin-based paints), which contain very toxic and hazardous chemicals that harm the environment, but also in water treatment applications and desalination, in which ZI can be applied to membranes for improved water desalination and treatment by preventing biofouling (Sadan et al., 2022; Xu et al., 2021; Yang et al., 2009; Zheng et al., 2017).

Polybetaines are the most used category of ZI in the majority of biofouling applications and studies. This is because of their superb hydration capabilities and net neutral charge, which work in harmony to prevent adhesion and proliferation of cells leading to efficient resistance to biofouling caused by cells. Briefly, the mechanism through which ZI polymers act as antibiofouling agents is by forming a charge-neutral surface with a very high hydration layer. This hydration layer is formed due to electrostatic interactions between the water molecules and ZI polymers on the surface and it prevents adhesion of negatively charged cells (Harding & Reynolds, 2014). Consequently, unlike antimicrobial agents, which either actively kill bacterial cells or prevent their growth, ZI-coated surfaces only inhibit the adhesion of bacterial cells through their hydration layer, consequently preventing their subsequent attachment (Li et al., 2020; Mi & Jiang, 2014). In the coming paragraphs, different fields, and applications where ZI polymers and their antibiofouling capabilities will be discussed.

Studying the antibiofouling of bacterial cells by ZI-coated surfaces on short- and long-run processes has received mixed outlook. [Marré Tirado et al. \(2016\)](#) studied polyamide RO membranes modified with ZI monomers 2-[(methacryloyloxy)ethyl] dimethyl-(3-sulfopropyl) ammonium hydroxide. The group measured the water contact angle, which indicated that the modified surface had become more hydrophilic compared to the pristine membrane. They also measured the bacterial deposition coefficient and saw a significant drop with the modified membrane, indicating fewer bacterial cells being able to attach and deposit on the surface of the coated membranes. Note that in this study, the ZI application did not lead to complete inhibition of bacterial adhesion. These results show that the ZI-modified RO membranes used in their study are able to improve the biofouling resistance properties by making the surface more hydrophilic and less favorable for bacterial cell adhesion. Surprisingly, the group saw that the antibiofouling properties of these modified membranes only lasted for a short term (first 10 h of the experiment) but could not solve biofouling issues in the long term. The group explained the observed phenomenon by saying that the surface modifications of the membranes were not enough to completely block bacterial cell adhesion, which eventually led to accumulation of bacterial cells and formation of biofilms on the modified surfaces, leading to biofouling in the long term ([Marré Tirado et al., 2016](#)). The group associated the failure to preventing biofouling in the long term to the conditioning capabilities of the bacterial cells with the modified surface first leading to adhesion and then to alteration of the physicochemical surface properties, eventually leading to biofilm formation and biofouling ([Harding & Reynolds, 2014](#); [Marré Tirado et al., 2016](#)).

Another group that studied the effects of ZI in both the short term and long term was Shivapooja's group. They tried overcoming the issue of long-term biofouling by applying uniaxial mechanical strain, which deformed the surface and increased its elastic energy, which in turn destabilized the biofilm-substrate adhesion and effectively detached the accumulated biofilms from the surface. Although their study was done on ZI-coated elastomers, it has been previously shown that applying a type of mechanical force on filtration membranes is also capable of controlling biofilm formation ([Zhang et al., 2017](#)). Thus the pSBMA-modified silicone elastomers were shown to have fouling-release functionality, a feature that could possibly be applied in manufacturing environmentally friendly coatings for biofouling management in the water filtration and other industrial fields ([Shivapooja et al., 2015](#)).

[Wu et al. \(2018\)](#) also studied the effectiveness of ZI modifications in both short and long terms. They monitored ZI-grafted textiles for bacterial adhesion in an attempt to industrialize the technology. The group successfully

grafted pSBMA ZIs onto cotton fabrics and showed a 99% drop in bacterial attachment in both short term (24-h period) and long term (120 h) as compared to nongrafted textiles. Here, the group similarly attributed the increased resistance to biofouling to the high hydrophilicity and water-binding capability of pSBMA via ionic salvation, upon measuring the water contact angle and wicking time (which is a measure of the time it takes for the contact angle to drop to 0 degrees). These studies demonstrate that ZI polymers have the ability to resist the adhesions of prokaryotic cells to form biofilms in the long and short term and that they exhibit versatility in terms of wide range of applications; thus they can potentially be incorporated into membranes and water treatment systems.

Many groups have studied how modifying currently available surfaces and membranes can significantly increase biofouling resistance in comparison to the pristine unmodified ones. Wang et al. (2016) studied the antibiofouling feature of ZI by showing that pCBMA-modified nanofiltration membranes exhibited 99% less adhesion of both Gram-negative and Gram-positive microorganisms compared to pristine membranes. The group attributed their findings to different mechanisms of ZI, which were at play to prevent such significant resistance to biofouling. First, they measured lower water contact angles on the ZI-modified membranes compared to the pristine ones, which indicated higher hydrophilicity and better surface hydration. Second, the group also measured the zeta potentials and found that the ZI-modified membranes had a near-neutral surface charge compared to the pristine membranes, which were negatively charged. The near-neutral charge of the modified membranes was attributed to the dissociation of the carboxylic acid groups and protonation of amine groups. The near-neutral charge and high hydration levels were postulated to be the reasons for the ZI-modified membranes to be highly resistant to bacterial cell adhesion and biofilm formation.

Saffarimiandoab et al. (2019) investigated commercial polyamide RO membranes by modifying them with SB zwitterions. Their group tested five different marine bacteria and showed significantly higher antibiofouling properties and resistance to biofilm formation on the modified RO membranes than unmodified ones, which were highly prone to biofouling. They attributed these findings to the formation of a hydration layer on the surface of the coated membranes by ZI groups, which created a strong energy barrier that prevented the adhesion and proliferation of bacterial cells. Shafi et al. (2015) studied the biofouling properties of commercial RO membranes by modifying them with CB zwitterions. The group found that such modifications lowered the adhesion of common marine prokaryotes, such as *Pseudomonas aeruginosa* and *Bacillus licheniformis*, to the ZI-modified RO membranes by 98% compared to their unmodified counterparts. They also

attributed this finding to the presence of a strongly adhered hydration layer onto the surface created by the higher electrostatic interaction of ZI moieties with ambient water. Once a tough hydration layer has been formed, adsorption of bacterial cells onto the surface of the CB-modified RO membranes is reduced, and surface-bacterial interactions are minimized (Shafi et al., 2015). Shen et al. (2013) modified commercially available PVDF membranes with PDMAEMA ZI moieties, which significantly increased their antibiofouling properties, leading to complete suppression of bacterial adhesion compared to the pristine PVDF membranes. Here, the group attributed the low biofouling findings to the segregation behavior of hydrophilic PDMAEMA chains, which had an enthalpic preference for being oriented toward the water-polymer interface and were involved in creating a strong hydration layer (Shen et al., 2013).

In addition to the membrane applications of ZI, the usefulness and versatility of ZI coatings could also be implemented in a variety of fields and industries. Xu et al. (2014) tried implementing ZI coatings in the contact lens industry by coating commercial contact lenses with pMPC. They showed that the modified lenses were 70% more efficient in decreasing bacterial adhesion compared to uncoated lenses. This could have an important role in preventing eye infections, which are of high-risk incidence in contact lens users. The team attributed the observed finding to the higher wettability of the coated lenses compared to pristine lenses, saying that the higher availability of free water molecules could have caused the resistance to bacterial adhesion and fouling. Kang et al. (2016) investigated the possible benefits of ZI coatings in dentistry. The group coated tooth enamel with pMPC and successfully prevented the adhesion of oral bacteria, such as *Streptococcus mutans*, that cause dental and periodontal diseases. The researchers' explanation for the observed phenomenon was that the pMPC coating interfered with protein-mediated bacterial adhesion, leading to inhibition of microbial attachment.

Many research groups have repeatedly shown that ZI polymers have increased biofouling resistance in comparison to other currently used anti-foulants. Modifying currently available membranes with ZI polymers further enhances their biofouling resistance compared to their pristine unmodified counterparts. In most situations the observed enhancement in biofouling resistance was attributed to the formation of a strong water barrier and the presence of a near-neutral charge. These two features of ZI polymers work harmoniously to repel bacterial cells from adhesion, proliferation, and subsequent biofilm formation, leading to efficient resistance to biofouling caused by bacteria. Consequently, different applications and fields could benefit from the versatility of polybetaine and polyampholyte ZI coatings to enhance biofouling resistance caused by prokaryotic cells.

2.5.2 Zwitterionic polymers and their interaction with eukaryotic cells

Biofouling also encompasses the adhesion and proliferation of eukaryotic cells onto surfaces. ZI-coated antibiofouling membranes are not commonly used to prevent eukaryotic cell adhesion. Instead, they are commonly studied for their biofouling properties with regard to eukaryotic cells, except for unicellular eukaryotes, which can behave similarly to prokaryotes. Unicellular eukaryotes, like single-cell marine algae, follow a similar sequence of adhesion steps as prokaryotic cells, in which adsorbed organic and inorganic molecules recruit these unicellular eukaryotic cells, leading to adhesion and proliferation. But as was mentioned previously, the process is more complicated in complex multicellular eukaryotic organisms, such as humans and animals. Here, multiple serum proteins, ECM components, and signaling pathways are involved, which first lead to adhesion of the eukaryotic cell to a surface, followed by pathways that subsequently lead to its proliferation and viability.

Many groups have studied the negative and positive effects of ZI-coated surfaces on biofouling by eukaryotic cells, but there are no studies of biofouling on membranes with eukaryotic cells. Therefore this section will first tackle the interactions of ZI-coated surfaces with microbial eukaryotes, followed by their interactions in more complex organisms, such as humans and other animals. We will also discuss the applications of biocompatible ZI surfaces and their benefits by selectively enhancing the adhesion of specific human cells onto ZI-coated surfaces, not directly related to membrane fouling.

ZI-coated surfaces were shown to inhibit the adhesion of marine eukaryotic cells, such as single-cell algae. As was mentioned previously, biofouling in marine environments is a global problem and is caused not only by prokaryotic microbes but also by marine eukaryotic microbes. In a study by [Dai et al. \(2019\)](#), the team successfully showed that such coatings effectively inhibit the adhesion of *Navicula incerta*, a diatom that is commonly found in marine environments and a major contributor to biofouling in these settings. Similarly to previous studies of biofouling prevention in marine environments, [Dai et al. \(2019\)](#) attributed the adhesion prevention of diatoms to the enhanced surface hydration of ZI-coated surfaces through their increased ability to strongly capture water molecules.

[Xu et al. \(2021\)](#) showed that coating marine surfaces with vertically arranged nylon fibers embedded with pSBMA ZI polymers was successful in inhibiting the adsorption of diatoms and mussels, which create plaques and lead to biofouling. The team hypothesized that the vertical arrangement of very thin fibers prevented the adhesion of diatoms that were larger in size. They also postulated that the vertical arrangement also made it unfavorable for mussels

to adhere. In addition to the vertical organization of the coatings, the group attributed the findings to the strong hydrophilicity and wettability of the pSBMA-coated fibers, which significantly decreased the adhesion capability of diatoms and mussels (Xu et al., 2021). The team also studied the stability of the coatings over a period of 30 days and found that such coatings were significantly stable for the whole duration of the study, as they retained more than 96% stability in artificial seawater environments, making them a cost-effective solution as antifouling agents (Xu et al., 2021). Additionally, Zhang et al. (2012) created hybrid ionic-covalent crosslinked double network hydrogels using sodium alginate and CB zwitterions and studied their antifouling properties. The researchers showed that the hybrid hydrogels exhibited exceptional antifouling properties and were capable of resisting the adsorption of different types of eukaryotic cells, including two types of algae: *Chlorella vulgaris* and *Microcystis aeruginosa*. The researchers attributed the findings to the strong affinity of CB polymers to water molecules, which in turn made the coatings highly hydrophilic, consequently hindering the fouling by the algal cells (Zhang et al., 2021). Carrying on with eukaryotic microbes, Knowles et al. (2019) investigated the adhesion prevention of fungal spores onto silica nanoparticles modified with SB zwitterions. The group used *Epicoccum nigrum* fungal spores to evaluate the efficiency of silica/SB nanoparticles against biofouling and found that the hybrid particles significantly decreased the adhesion of hydrophobins, which are adhesive proteins that are required by fungal spores to promote adhesion and attachment. This inhibitory feature decreased the incidence of biofouling and spore adhesion. The researchers also attributed their findings to the strong hydration capability of SB. Similarly to biofilms caused by prokaryotic microbes, yeast cells, such as those of *Candida albicans*, can also exhibit biofilm formation, specifically on hydrophobic surfaces, through an analogous multistep process, which initially involves hydrophobic and electrostatic interactions, followed by a stronger adhesion through membrane glycoproteins and formation of microcolonies with subsequent formation of more structured matrices that are similar to biofilms in their complexity (Lazarin et al., 2013; Masotti et al., 2020). Consequently, Lazarin et al. (2013) investigated acrylic surfaces modified with SB zwitterions and attributed the decreased levels of *C. albicans* adhesion and biofilm formation to the surface wettability and high hydrophilicity of the ZI-modified coatings.

Multiple groups have studied the effect of ZI-coated surfaces and their interactions with animal and human cells. When it comes to integrating ZI technologies into firsthand applications, such as coatings of implants, biocompatibility is a major concern. Lack of biocompatibility impedes the implementation of ZI in implantable medical devices. Many groups have investigated the biocompatibility of ZI coatings in different ways. For

example, [Zhang et al. \(2021\)](#) created hybrid hydrogels composed of sodium alginate and CB zwitterions and performed in vitro cytotoxicity experiments using mouse fibroblasts to check for their biocompatibility by measuring the percent cell viability. They also studied the hybrid hydrogels by performing in vivo experiments, in which the sodium alginate/CB hydrogels were implanted under the skin of mice for a period of 1–4 weeks, after which tissue samples from the area surrounding the implant were collected and studied for pathological abnormalities. Both in vitro and in vivo experiments showed that the hybrid hydrogels were highly biocompatible with the cells, remaining over 80% viable.

[Li et al. \(2020\)](#) studied the interaction of ZI-coated surfaces with eukaryotic cells. They showed that SBMA-coated surfaces are highly biocompatible and could potentially be integrated into wound-dressing films to help in wound healing. [Zhang et al. \(2013\)](#) investigated this property by monitoring the host reaction to ZI-coated hydrogels on subcutaneous implantation. The group demonstrated that the common events that are known as foreign-body reactions that follow implantation of foreign biomedical devices, such as hydrogels, not only were absent when the latter were coated with CBMA ZI polymers and implanted into mice, but also promoted angiogenesis, a process that the body uses to develop new blood capillaries for increased blood circulation and delivery of nutrients and oxygen.

The cytocompatibility of SBMA-coated membranes was studied by [Liu et al. \(2014b\)](#), who showed that two-dimensional and three-dimensional cell cultures looked like controls and had typical cell morphologies and features. Nanoparticles composed of ZI polymer shells have been shown to effectively deliver encapsulated drugs, therapeutic proteins, and even siRNA ([Li et al., 2020](#); [Yang et al., 2009](#)). [Liu et al. \(2014a\)](#) further investigated the possibility of using such drug delivery systems by studying their blood compatibility and cytocompatibility. The group showed that cellulose membranes modified with ZIs of SB or PC types significantly decreased the nonspecific adhesion of proteins and platelets found in blood, owing to their surface wettability characteristics. The researchers also showed that such features were found to be comparable to PEG, the benchmark antibiofouling surface that is currently used. These findings make ZI coatings a promising substitute for PEG.

Titanium alloys modified with pCMB were shown to lower nonspecific cell adhesion and increase deposition of calcium ([Nishida et al., 2017](#)). This finding has encouraging consequences in the field of orthopedics, where titanium alloys are commonly used as implantable orthopedic materials and where successful integration of implants into the host tissue is important. In contrast to most studies, which focus only on preventing cell adhesion to

prevent biofouling, [Ji et al. \(2012\)](#) used another approach, in which they first inhibited all nonspecific eukaryotic cell binding and then selectively stimulated the adhesion of specific endothelial cells of interest onto ZI-coated surfaces to further stimulate their adhesion and proliferation on the implant. Therefore the group first exploited and made use of the high antifouling property of CB zwitterions to initially prevent the nonspecific adhesion and growth of smooth muscle cells. Upon inhibition of nonspecific cell binding, the researchers then introduced into the system a specific endothelial cell–selective bioactive peptide that provided specific signaling and stimulation for the proliferation of endothelial cells and successfully enhanced their attachment and growth on these cardiovascular implants coated with the ZI polymers.

Consequently, when it comes to eukaryotic cells, ZI polymers can have different uses depending on the desired outcome. But on the basis of these studies, ZI can prevent bacterial proliferation and be safer for human and other mammalian cells; thus they show promise for water treatment applications. Although there have been studies related to biofouling resistance of ZI-coated membranes and surfaces, there is still a huge gap in knowledge regarding the antibiofouling properties of ZI on different membranes used in water filtration. Furthermore, prokaryotes are not the only contaminants found in water. Further studies need to be done to unravel how ZI-grafted membranes interact with eukaryotic cells. The fact that ZI-coated surfaces resist biofouling only through the presence of a strong hydration layer, without being harmful and cytotoxic, shows that these coatings and polymers are biocompatible and could have a wide range of applications that still need to be explored.

2.6 Conclusions and further remarks

In conclusion, in this chapter we presented various types of ZI materials with multiple unique features in terms of their hydration, hydrophilicity, and surface charge properties. The choice of ZI to be used by researchers in each specific field depends on the outcome and functions they are seeking. In fact, the only common feature of all the different ZIs is that their mode of action to prevent fouling of organic, inorganic, and biomolecules is through the presence of a very strong hydration barrier that provides an excellent hydrophilic surface, which in turn prevents the adsorption and deposition of such molecules. This higher surface wettability of ZI polymers is due to the presence of both cationic and anionic moieties, which attract a large number of water molecules around the polymeric chains through charge-dipole interactions and hydrogen bonding. Throughout the chapter we demonstrated the mechanisms of interactions of ZI-grafted membranes with inorganic

molecules, organic molecules, and biomolecules. We have also covered different fields and uses of ZI polymers showing their versatile applications. Through discussion of the findings from different fields and research groups, we showed that once a membrane has been coated with ZI polymers or even modified with a ZI polymer, the fouling resistance (i.e., inorganic, organic, and biofouling) performance of the surface can be significantly improved in comparison to pristine unmodified membranes or other currently available options. We were also able to demonstrate that the overall efficacy and performance of ZI-grafted membranes is prolonged in comparison to their uncoated counterparts, a feature that could be useful in lowering the operation costs of water filtration systems.

Implementing ZI for a long-term solution to fouling prevention remains a challenge in multiple fields. When it comes to more complicated environments, the self-hydration properties of ZI materials might be affected and compromised by these settings. For example, the bonding of salt ions with ZI polymer can change the ordering of water molecules at the interface of the water and ZI polymer, thus bridging the organic foulant adsorption and worsening the lubrication performance of ZI polymer surfaces. Similar difficulties are faced when bacterial cells breach the surface hydration layer or even adapt to the ZI-coated surface, which can lead to attachment, proliferation, and biofilm formation in the long run.

Since ZI technologies are relatively new, there is a lot to be explored. For example, many studies demonstrated that ZI-coated surfaces have excellent antifouling behaviors, yet a reliable functionalization technique for ZI polymer coating on diverse substrates or membranes has yet to be developed and standardized. This is because different types of ZI polymers might have different affinities to specific substrates. For example, CB can be easily functionalized on varied membrane substrates through the grafting-from strategy, owing to the presence of carboxyl groups compared to SB and PC. However, this method for membrane modification inevitably causes the reduction of membrane permeability, which requires further investigations. Moreover, previous studies only confirmed that SB-based ZI could be promising for the development of scaling-resistant desalination membranes. Since there is a vast library of ZI polymers, each having different properties (i.e., hydration capability and charge density), further studies should be done to find the optimal ZI structure or properties for specific applications. In addition, current studies have analyzed the underlying scaling mechanism only from the perspective of surface thermodynamics. However, the mechanisms that are involved in the control of mineral scaling with ZI polymers is still far from being well understood. For example, the interaction between multiple scale-forming ions and ZI polymers during the scaling process is still unknown. Additionally, it has been demonstrated that pCBMA and pSBMA, in different

environmental conditions, cause different orientations of free water molecules. Hence the mechanism of protein-fouling resistance by ZI polymers needs further research. Future studies on the interaction of water with ZI polymers under different conditions could provide an in-depth understanding of the antifouling mechanisms. Finally, owing to the versatility of ZI polymers, their use can be exploited beyond water filtration membrane applications and enable other fields of study to benefit from its excellent properties. One such field could be that of bioengineering, since only a few studies have exploited the possibility of using ZI-coated surfaces as a platform for the specific adhesion and proliferation of cells of interest. This feature needs to be further investigated, since it could have drastic implications to help alleviate the shortage of organs for transplantation and may also be used for faster recovery and healing of patients after surgery.

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