IOP Publishing Journal of Physics D: Applied Physics
J. Phys. D: Appl. Phys. **52** (2019) 403001 (17pp) https://doi.org/10.1088/1361-6463/ab2cbc

Topical Review

Fundamentals and applications of zwitterionic antifouling polymers

Yanxian Zhang[1,5,6], Yonglan Liu[5,6], Baiping Ren[5], Dong Zhang[5], Shaowen Xie[1,5], Yung Chang[2], Jintao Yang[3], Jiang Wu[4], Lijian Xu[1,7] and Jie Zheng[5,7]

[1] Hunan Key Laboratory of Biomedical Nanomaterials and Devices, College of Life Science and Chemistry, Hunan University of Technology, Zhuzhou 412007, People's Republic of China
[2] Department of Chemical Engineering and R&D Center for Membrane Technology, Chung Yuan Christian University, Taoyuan 320, Taiwan
[3] College of Materials Science and Engineering, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China
[4] School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, Zhejiang 325035, People's Republic of China
[5] Department of Chemical and Biomolecular Engineering, The University of Akron, Ohio 44325, United States of America

E-mail: xlj235@163.com and zhengj@uakron.edu

Received 13 August 2018, revised 29 April 2019
Accepted for publication 25 June 2019
Published 26 July 2019

Abstract

Zwitterionic materials as a new class of emerging materials have recently been developed and applied to a broad range of biomedical and engineering applications. Zwitterionic materials possess a unique molecular structure combining both cationic and anionic groups with overall charge neutrality and high hydrophilicity. In this review, we first provide the structure-property relationship of the zwitterionic materials at molecular level, from a molecular simulation viewpoint. Then, we discuss the recent experimental developments in the preparation, properties, and applications of zwitterionic materials, with a particular focus on their antifouling properties on coating surfaces and with additional functionality and applications. Finally, we offer our personal viewpoint of current challenges and future directions in this emerging area. Our goal is to introduce the current status of this type of new zwitterionic materials to researchers from different areas and motivate them to explore all the potentials.

Keywords: zwitterionic materials, antifouling, materials desgn, nonspecific protein interactions, biomedical materials

(Some figures may appear in colour only in the online journal)

1. Introduction

Naturally occurring zwitterions (e.g. glycine betaine and β-alanine betaine) are very common moieties found in cell membranes, proteins, or osmolytes [1–3]. These zwitterions often exhibit a variety of molecular structures, and accordingly play distinct functions in biological process via their different interactions with or stimulation by environmental factors such as ions, pH, and functional groups outside proteins [4]. So, inspired by natural evolution, zwitterionic polymers, as analogues of naturally occurring biological molecules, are designed and synthesized with different zwitterionic moieties, which have an equal number of cationic and anionic groups

[6] The authors equally contributed to this work.
[7] Authors to whom any correspondence should be addressed.

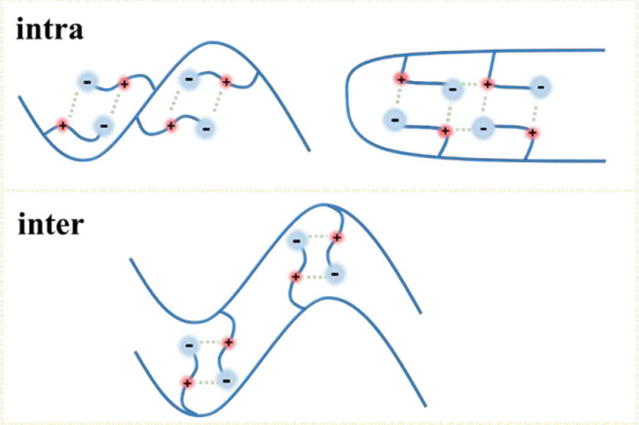

Figure 1. Different interaction modes between polymeric zwitterions.

in the same polymer chains. Such unique combination of two oppositely charged groups in the same moiety empowers zwitterionic polymers with unique structure and property features, e.g. overall charge neutrality, high hydrophilicity, strong dipole pairs, and anti-polyelectrolyte effect [5]. These features make zwitterionic polymers promising biomaterials to fight against long-term fouling problems. Apart from antifouling-related applications, the unique structures and chemistries of zwitterionic materials also offer other properties and functions for other application, e.g. ionic liquid for polyelectrolyte systems [6, 7], drug/gene delivery system with supreme cell uptake efficiency and nontoxicity [8], and smart materials with pH-, solvent-, thermal-responsive property [9–11]. As a generally-accepted water barrier principle, the antifouling property of zwitterionic polymers fundamentally originates from a tightly and stably bounded water layer near zwitterionic polymers via strong electrostatically induced hydration [12]. The hydration-induced antifouling principle is also confirmed by hydrophilic polymers such as poly(ethylene glycol) (PEG) [13], poly(acrylamides) [14], and poly(acrylates) [15] due to their strong hydration via hydrogen bonding [16], which are relatively easy to break and reform as compared to ionic solvation [17]. Strong hydration requires large free energy for foulants to be adsorbed on the surface made of zwitterionic and hydrophilic polymers [16, 18]. Moreover, the formation of dipole pairs between intra- and inter-zwitterionic groups also leads to the self-association of zwitterionic polymers to some extents [19] (figure 1). In this way, different from polyelectrolytes containing anionic groups, or cationic groups, or non-equal numbers of cationic and anionic groups, zwitterionic polymers display the anti-polyelectrolyte behavior [20, 21], i.e. zwitterionic polymer chains shrink in water but stretch in salt solution, making them to have the greater solubility in salt water than in pure water. Thus, from molecular simulation, *in vitro*, and *in vivo* experiments, zwitterionic polymers have demonstrated their excellent antifouling property, comparable to or even better than PEG-based hydrophilic and polyelectrolyte-based polymers for resisting protein adsorption [22–24], cell adhesion [25, 26], and bacterial attachment [27–30].

The first synthesis of zwitterionic polymers could be traced back to 1950s [31], including methacrylic acid-*stat*-2-(dimethylamino)ethyl methacrylate copolymers [32], acrylic acid-*stat*-2-vinylpyridine copolymers [33], and acrylic acid-*stat*-2-(diethylamino)ethyl methacrylate copolymers [34]. Initial studies of these zwitterionic polymers focus primarily on polymer design, synthesis development, and physicochemical characterization, while their corresponding applications mainly target wastewater treatment, ion exchange, pigment retention, and solid conditioning by making use of their ion-binding/chelation features [35]. The first discovery of antifouling property of zwitterionic 2-methacryloyloxyethyl phosphorylcholine (MPC) was reported by Ishihara and coworkers [36], but antifouling performance of zwitterionic MPC copolymers was not optimized yet and only worked for protein resistance from single protein solutions. Since then, a different family of zwitterionic polymers have been developed and proved for their improved antifouling capacity of efficiently resisting nonspecific protein adsorption from complex media. These zwitterionic polymers are generally formed or copolymerized by five common zwitterionic moieties, carboxybetaine (CB), sulfobetaine (SB), phosphatidylcholine (PC), Cysteine (Cys), and 3-(1-(4-vinylbenzyl)-1H-imidazol-3-ium-3-yl)propane-1-sulfonate (VBIPS) (figure 2). The past decade has witnessed the growing interest in (1) development of different zwitterionic antifouling coatings to improve the reduction of nonspecific protein adsorption [12, 24, 37]; (2) mechanistic study of the structure-hydration-antifouling relationship of zwitterionic polymers [18, 38, 39]; (3) *in vitro* antifouling applications of zwitterionic polymers for membrane separation/filtration [40], wastewater treatment [41], biosensors [42, 43], drug delivery carriers [44]; (4) *in vivo* biomedical applications of zwitterionic polymers for implants [45], wound dressing [46], blood purification [47], and contact lenses [48]; (5) computational study of the structural-dependent hydration, ionic association, and protein interaction of zwitterionic polymers [49–55], and (6) apart from antifouling property, exploration of additional functionality (e.g. antimicrobial [28], friction [56], actuation [57, 58], self-healing [59]) of zwitterionic polymers.

While the acceleration in scientific publication in figure 3 has shown significant progress and high impacts of zwitterionic polymers on both fundamental and practical research, zwitterionic antifouling polymers as a relatively new class of biomaterials are still a subject under less investigation, as compared to intensive research on PEG-based and other antifouling materials. Thus, the more and continuous efforts are still needed to develop alternative antifouling materials. In this review, we strive to provide an updated summary of the research related to zwitterionic antifouling polymers, covering basic antifouling concepts, dual/multiple functionality, *in vitro* and *in vivo* applications, and computational materials design. Finally, we discuss some of the persistent technological barriers that still remain and the research directions that should be undertaken to overcome these barriers. Hopefully, this review will stimulate further computational and experimental efforts to obtain new knowledge (synthesis/coating methods and polymer systems) for exploring all the potentials

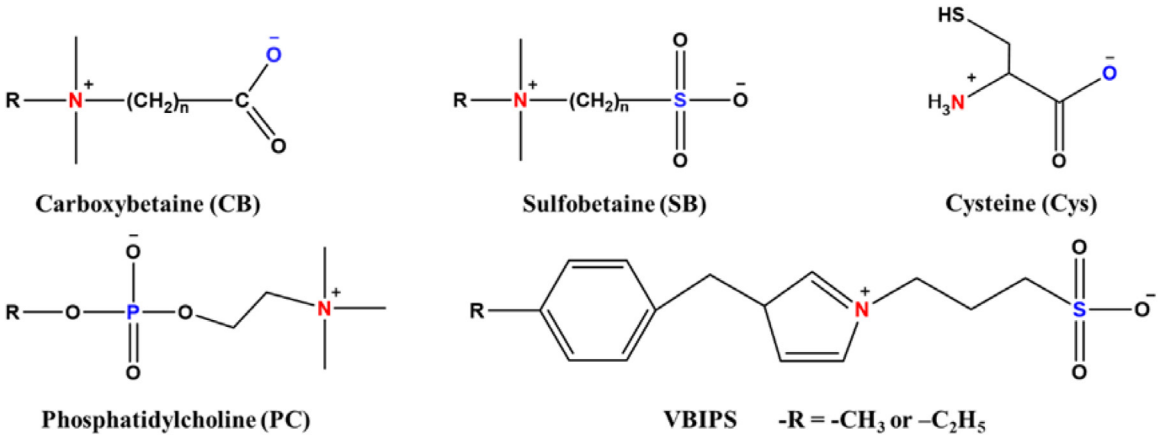

Figure 2. Representative zwitterionic moieties.

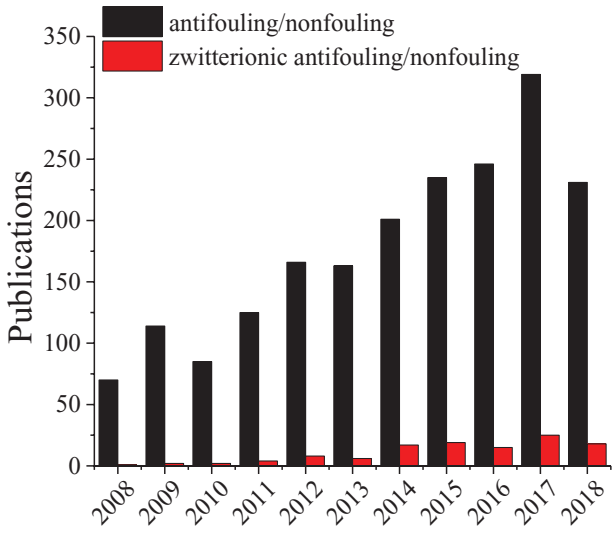

Figure 3. Number of SCI-index papers in the field of antifouling/nonfouling and zwitterionic antifouling/zwitterionic nonfouling during the past decade, as searched by the keywords 'antifouling', 'nonfouling', 'zwitterionic antifouling', and 'zwitterionic nonfouling', from ISI database.

of other antifouling materials (e.g. nanoparticle, peptides, lipids, and their hybrids with polymers).

2. Fundamental and computational aspects: structural-dependent antifouling activity of zwitterionic polymers

While a number of computational and experimental studies have been undertaken with prevalently promising findings, the results have merely empirical character and are not satisfactory from a fundamental viewpoint. On one hand, different zwitterionic polymers are so different in structures, but all of them are highly resistant to the attachment of proteins, cells, and bacteria. On the other hand, small differences in structures (e.g. change in carbon space length, pendant group, and charge type/pair/distribution) of zwitterionic polymers can also lead to large enhancement in antifouling performance. These phenomena strongly suggest the structural-dependence of zwitterionic polymers on their hydration structures, hydration dynamics, and degrees of interactions with water molecules and foulants. While zwitterionic polymers comprise a large library of molecules with different, physicochemical properties of zwitterionic groups, these polymers are mainly built from five common zwitterionic moieties. It still remains a great challenge to derive the chemical structure–antifouling property relationships of zwitterionic polymers based on the limited variations in zwitterionic groups, i.e. combinations of anionic/cationic types and topological structures of zwitterionic groups. Thus, molecular modeling and simulations are a powerful and suitable tool that enables to capture subtle differences in structural-dependent properties of materials at atomic length- and time-scale.

2.1. Zwitterionic identities

Intuitively, from a structural viewpoint, zwitterionic types and structures are two key properties for the antifouling performance of zwitterionic polymers. As shown in figure 1, the five zwitterionic moieties exhibit completely different structures. Molecule dynamics (MD) simulations have shown that, on one hand, all of the different zwitterionic moieties display strong binding with water molecules (i.e. strong hydration) that is dominated by electrostatic interactions similar to ionic hydration [51]. On the other hand, variations of function groups, charge density, and separation distance of zwitterionic moieties also influence their hydration free energy, hydration dynamics, and hydration structures at atomic details. In addition, the presence of cationic and anionic groups in zwitterionic moieties enables to self-associate zwitterionic moieties together via electrostatic interactions, and such self-association behavior has been observed in all zwitterionic materials. Different degrees of self-association capacity not only offer distinct functions (e.g. stimuli response [57, 58, 60, 61], anti-polyelectrolyte effect [20, 62], lower/upper critical solution temperatures [63–65]) of zwitterionic materials, but also affect their antifouling properties. Thus, hydration, ionic interaction, and self-association are the three key parameters in controlling the protein resistance capability of zwitterionic materials.

CB and SB are the two most commonly used zwitterionic moieties for (co)polymerization into different CB- and

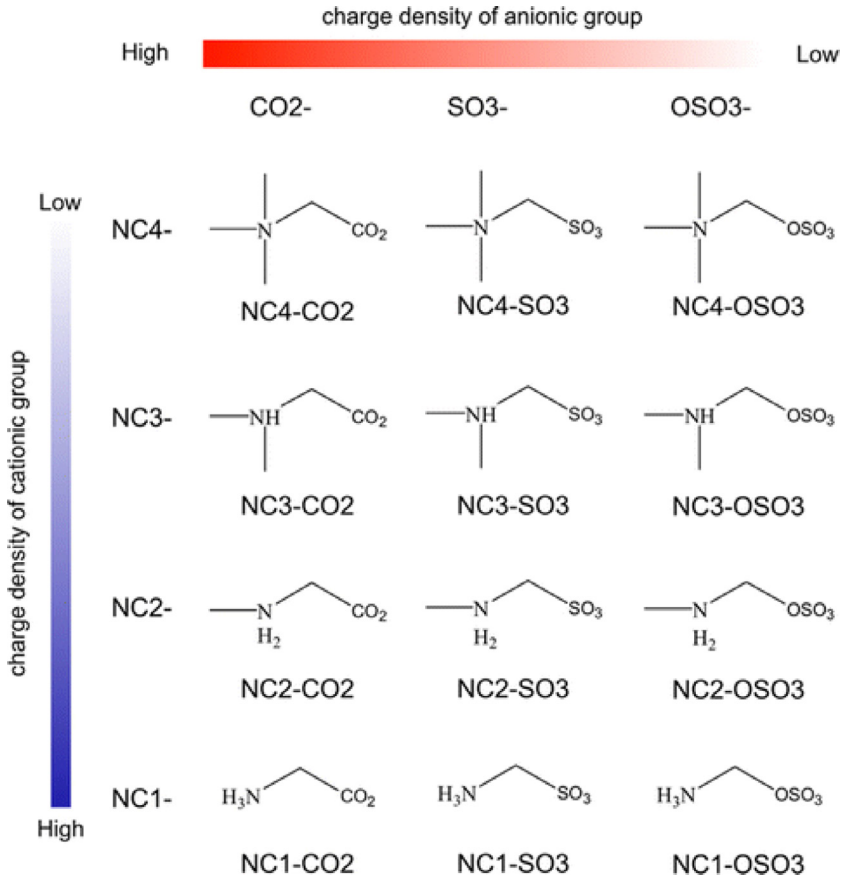

Figure 4. Twelve zwitterionic moieties, each with a distinct combination of anionic and cationic groups. Reprinted with permission from [51]. Copyright © (2014) American Chemical Society.

SB-based zwitterionic polymers. CB moiety contains a cationic trimethyl ammonium group and an anionic carboxylic group, while SB moiety possesses a cationic trimethyl ammonium group and an anionic sulfonate group. So, SB moiety shares the same cationic group as the CB moiety, but has an anionic sulfonate group whose charge density is lower than that of the carboxylic group in CB moiety. Distinct structure makes SB-based materials with salt-responsive properties and CB-based materials with ease of functionalization. Since sulfonate group of SB moiety has less charge density than the carboxylic group of CB moiety, (i) SB moieties tend to attract more water molecules than CB moieties, while CB moieties interact more strongly with individual water than SB moieties [66]; (ii) SB moieties prefer to have stronger association with chaotropic cations (K^+ and Cs^+) than CB moieties, while CB moieties tend to associate with kosmotropic cations (Li^+ and Na^+) stronger than SB moieties [67]; and (iii) SB moieties exhibit relatively stronger self-association property than CB moieties, probably because SO3 possess the stronger charge density than CO2 [52]. While SB and CB moieties have distinct charge identify and density, all of SB- and CB-derived materials possess strong hydration, which is necessary for resisting nonspecific protein adsorption. However, a lack of self-association capacity makes CB materials more effective to resist unwanted protein adsorption than SB materials with moderate self-association property. Additionally, CB materials with moderate charge strength and density could better mimic the zwitterionic feature of protein surfaces than SB materials. This also explains experimental results that CB materials generally behave more inertness than SB materials in complex media (e.g. human blood plasma/serum, whole blood, and tissues) [50, 51, 68].

Apart from typical CB and SB moieties, a complete combination of three anionic groups: carboxylic (CO2), sulfonate (SO3), and sulfate (OSO3) with four cationic groups: quaternary ammonium (NC4), tertiary ammonium (NC3), secondary ammonium (NC2), and primary ammonium (NC1) produced 12 different zwitterionic moieties, each with distinct chemical structure and charge density (figure 4). Overall, all of 12 different zwitterionic moieties (-238–303 kJ mol^{-1}) had the lower hydration free energy than a well-known ethylene glycol (EG4) moiety (-180 kJ mol^{-1}), indicating that ionic-induced hydration in these zwitterionic moieties has more favorable interaction with water molecules than hydrogen-bond-induced hydration in hydrophilic moieties. Among 12 zwitterionic moieties, a trend of hydration free energy can be observed in a decreased order in term of anionic group: OSO3 > SO3 > CO2, where NC3-OSO3, NC2-OSO3, and NC1-OSO3 (except for NC4 groups) had much lower hydration free energy than others by 30-87 kJ mol^{-1}, presumably because OSO3 group has the lowest charge density compared to other anionic groups. Differently, no trend was displayed in terms of cationic groups. Free energy calculation reveals that the hydration free energy of zwitterionic moieties largely

depends on the charge densities of the charged groups, particularly anionic groups have more predictable structure-property relationship, i.e. the lower charge density of anionic groups, the more favorable hydration free energy. Regarding the water dynamics around zwitterionic moieties, cationic-based NC1, NC2, NC3, and NC4 moieties allow to associate with water molecules in an increase order of NC1 (<5 water molecules) < NC2 (10–14 water molecules) < NC3 (~15 water molecules) < NC4 (~16 water molecules). These water association numbers appear not to largely depend on the types of cationic groups, and these associated water molecules tend to stay around the carbon atoms of NC2, NC3, and NC4 in an increased order of residence time of ~20, 25, and 25 ps, respectively. Different from hydration free energy, hydration structural and dynamic properties of these zwitterionic moieties are not sensitive to cationic groups. Moreover, the hydration-related properties are also affected by the self-aggregation of zwitterionic moieties. Strong self-aggregation is likely to be driven by electrostatic, dipole, and some hydrophobic attraction among zwitterionic moieties, and consequently these interactions would consume potential binding sites with water molecules, thus reducing zwitterionic-water interactions and leading to weak hydration. Among them, NC2 and NC3-based zwitterionic moieties displayed moderate self-associations, while NC4-based moieties, particularly NC4-CO2 moiety, have the least potential for self-association. Among 12 zwitterionic moieties, since NC4-CO2 and NC3-CO2 moiety have the highest hydration and the least self-association properties, both showed to have the unfavorable interaction with a model protein, demonstrating their strong ability to resist nonspecific protein adsorption.

2.2. Zwitterionic structures

Apart from different zwitterionic identities, zwitterionic moieties can also be varied by change their structures (e.g. separation distance between the charged groups), which would be expected to induce different hydration structures, hydration dynamics, and degrees of interactions with water and proteins. Carbon spacer length (CSL) is defined as the number of methylene groups of $(CH_2)_n$ between the anionic and cationic groups. Intuitively, variation of CSL is expected to change (i) the hydrophilicity/hydrophobicity ratio of the zwitterionic polymers and (ii) the flexibility of polymers, both of which will in turn affect polymer conformation and their interactions with water and protein. For instance, zwitterionic polymers with different CSLs could have different extents of hydrophobic interactions, while zwitterionic polymers with longer CSLs may have a larger chain entanglement and flexibility. While a number of experimental works have studied the effect of CSL of zwitterionic molecules on their bulk physicochemical properties [69], adsorbed protein conformation [70], mobility of ionic group [71], thermal stability of the material [72], and adsorption at the air–water interface [73], very few MD simulations have been conducted to examine how CSL changes affect the hydration–structure-interaction relationship of zwitterionic materials in bulk solution or at air/water interface. To our knowledge, only one MD study by Shao *et al* [53] has reported the effect of CSL on the hydration behavior of five CB molecules from structural, dynamic, and interaction aspects, where CSL is varied from 0 to 4. It was found that as CSL in CB moieties increases from 0 to 3, a number of water molecules around CB moieties increases monotonically from 22 to 32, residence time of water molecules around CB moieties (i.e. tendency of water molecules to stay around CB moieties) increases from ~8.6 ps to 37 ps, and hydration free energy significantly decreases from 270 kJ mol^{-1} to 0 kJ mol^{-1}, respectively. But, as CSL $\geqslant$ 3, further increase of CSL does not alter the hydration behavior of CB moieties. Such structural-induced hydration differences for zwitterionic polymers at nanoscale could account for different antifouling performance of zwitterionic polymers at macroscale.

From a structural viewpoint from molecular simulations, highly inert zwitterionic materials should have possess a high-charge-density anionic group and a low-charge-density cationic group, and such combination of zwitterionic pairs allows to form a strong hydration layer, disfavor self-association, and weaken interactions with proteins, all of which account for three design criteria of hydration, self-association, and protein interaction for zwitterionic antifouling materials.

3. Fundamental and experimental aspects: antifouling activity of zwitterionic polymer surfaces

Biomedical materials, particularly for (pre)clinical or implanted materials, should have a basic but important property of reducing foreign body reaction. So, combating the foreign-body response requires the coating surfaces to be inert or stealthy for preventing nonspecific protein adsorption at the first step. In past decades, solid surfaces coating with zwitterionic polymers have been regarded as a promising strategy for the creation of hydrophilic, biocompatible, inert (noninteracting) surfaces, which generally exhibit high surface resistance to biofouling formation, comparable to or even better than PEG-based antifouling materials that are susceptible to oxidation damage upon long-term use, thus losing their antifouling function [24, 74].

3.1. Enhanced surface hydration of zwitterionic polymer brushes

Inspired by the phospholipid structure on cell membranes, zwitterionic 2-methacryloyloxyethyl phosphorylcholine (MPC) moiety was first identified for its antifouling property. Protein resistance of MPC-based polymers is attributed to their similar structure to the polar group of phospholipids, which can further form the organized bilayer-like membrane structure and thus inhibit the surface interaction with proteins and cells [75]. Since then, a new class of zwitterionic moieties, such as phosphorylcholine (PC), sulfobetaine (SB), and carboxybetaine (CB), were designed, tested, and identified as basic building units for antifouling materials. A deeper understanding of protein resistance mechanism reveals that a tightly bonded water layer around antifouling surfaces is critical for

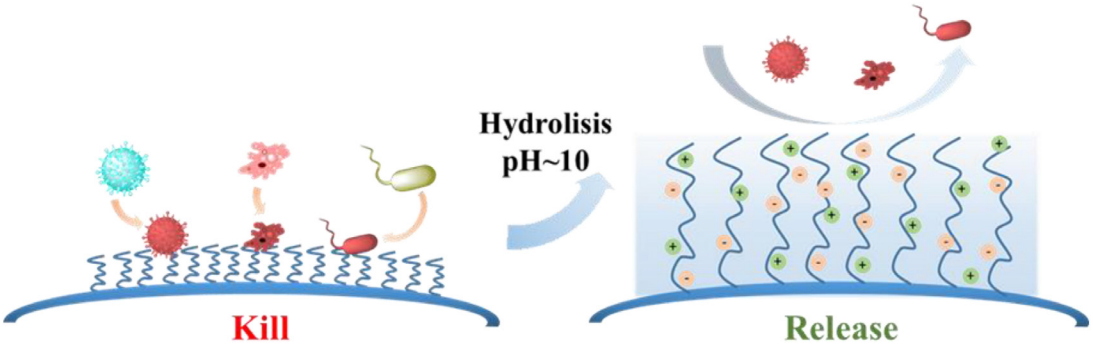

Figure 5. The 'kill-release' regeneration process of zwitterionic materials.

preventing proteins from approaching surfaces closely [76, 77]. By comparing the hydration of zwitterionic polymers and poly-hydrophilic materials, numerous studies have demonstrated that different from the water layer formed on hydrophilic materials via hydrogen bonding, the water layer formed on the zwitterionic polymer is more tightly bonded in larger quantity and higher quality, as a result of the electrostatically induced strong solvation [78].

Wu *et al* [79] compared the hydration characteristics of zwitterionic polySBMA and hydrophilic PEG antifouling materials by the spin–spin relaxation time (T_2) using the low-field nuclear magnetic resonance (LF-NMR). They found that zwitterionic polySBMA contained a much larger number of nonfreezable water than PEG, highlighting the stronger association of water molecules with zwitterionic $N^+(CH_3)_3$ and SO_3^- groups via electrostatic interactions. Leng *et al* [18] studied the real-time surface hydration of polySBMA and oligo (ethylene glycol) methacrylate (polyOEGMA) brushes in contact with proteins using the sum frequency generation (SFG) vibrational spectroscopy. The results showed that upon contacting with proteins, the water ordering was disturbed on polyOEGMA surface, but remaining unaffected on polySBMA surface. This indicates from another angle that polySBMA binds water molecules stronger than polyOEGMA. In parallel, Leng *et al* [80] prepared the mixed charged polymers at the equal molar of positively charged [2-(methacryloyloxy) ethyl]trimethylammonium chloride and negatively charged 3-sulfopropyl methacrylate potassium salt, and they found that interfacial water behavior on the 1:1 mixed charged polymer was similar to that on zwitterionic polymers, revealing the importance of charge neutrality in creating strong surface hydration. Ladd *et al* [24] performed a comparative study on six different polymers (i.e. polyOEGMA, polySBMA, polyCBMA) and self-assembled monolayers (i.e. OEG, mixed trimethylamine and sulfonic acid (TMA/SA), mixed trimethylamine and carboxylic acid (TMA/CA)) for testing their surface resistance to nonspecific protein adsorption from human serum and plasma. All polymer surfaces outperformed SAMs on nonspecific protein adsorption resistance due to the higher packing density. Among polymer surfaces, as a result, both zwitterionic polySBAA and polyCBAA present ultralow non-specific adsorption in 100% human serum (<50 ng cm^{-2} for polySBAA, <10 ng cm^{-2} for polyCBAA) and plasma (<10 ng cm^{-2} for polySBAA, immeasurable for polyCBAA). PolyCBAA surface outperformed polySBAA surface for protein resistance due to the stronger hydration layer around ionic groups. Further comparison between three polyCBAA surfaces with different carbon spacer lengths (i.e. methylene, ethylene and propylene) confirmed that the shorter CSLs (~1–2) the better protein resistance capacity in undiluted human plasma and serum (<5 ng cm^{-2}) [81]. Under optimal conditions, the highly enhanced surface hydration by zwitterionic polymer brushes could achieve nearly zero protein adsorption from undiluted human blood serum and plasma [82–84]. In addition to their ultra-low fouling property, zwitterionic polySBMA brushes are highly stable without undergoing significant oxidation or degradation in a wide range of ionic strength, pH values and temperature [85]. Zwitterionic CB group exhibits an acid-base equilibrium and is a great platform for coupling with primary amines (proteins or antibodies) to create ligand-functionalized materials in a nonfouling background, which could be used as highly sensitive biosensors for detecting specific proteins/antibodies in complex biological media (e.g. human blood, serum, plasma) with the improved false alarm [81, 86, 87].

Microbial adhesion and the subsequent biofilm formation are another critical issue for biomedical and industrial applications. Hypothetically, high surface hydration may have influence on microbial adhesion, but there is no direct correlation between protein resistance and microbial adhesion [88, 89]. Hydrophilic PEG-coated surfaces resist bacterial adhesion in a short term due to enzyme-catalyzed oxidation and instability. Cheng *et al* [27, 29] reported the resistance of bacterial adhesion and the prevention of biofilm formation by polySBAA and polyCBAA surfaces. As compared to PEG-coated surfaces, zwitterionic polySBAA- and polyCBAA-coated surfaces greatly suppressed 95% of microbial attachment up to 10 d [27, 29]. More importantly, a modified polyCBMA material was designed and possessed a switchable bacteria-killing and bacteria-releasing capability. The working principle is that a reversible lactonization reaction for CB esters occurs between a cationic ring form and a linear zwitterionic form, i.e. original CB esters contain high cationic charge density that enables to kill bacteria at its cationic state, but once it is hydrolyzed into a zwitterionic form under pH ~ 10 alkaline conditions whose nonfouling nature enables to release dead bacterial cells [90]. In this way, a single polyCBMA cationic derivatives surface can achieve bacteria-killing,

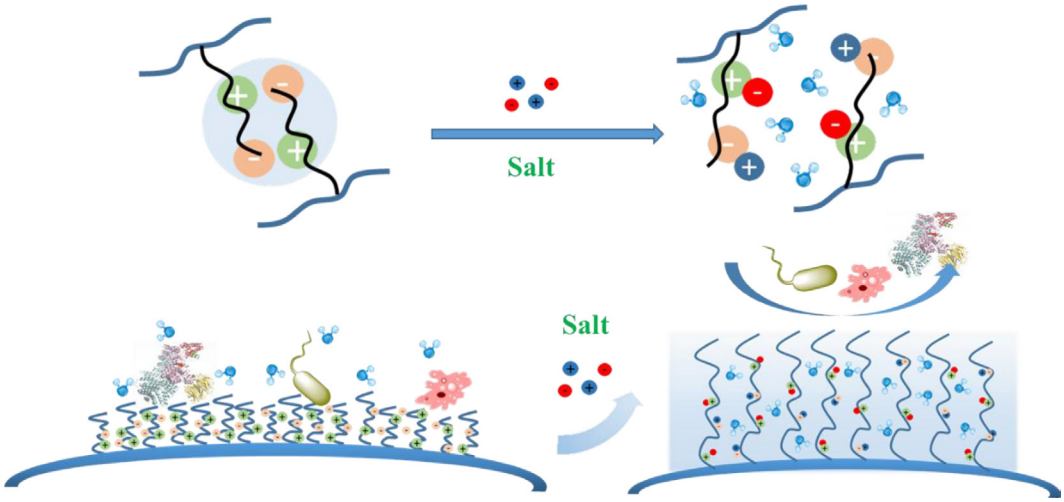

Figure 6. Anti-polyelectrolyte effect of zwitterionic polymers with reduced friction, enhanced wettability, and antifouling property in response to salts.

bacteria-release, and surface regeneration in a cyclic way [30]. So, zwitterionic materials offer a promising 'kill–release' strategy to construct dual-function antibacterial-antifouling surfaces, which can kill bacteria attached to their surface and then release the dead bacteria to regenerate a clean surface under an appropriate stimulus [91], thus maintaining long-term antibacterial activity (figure 5) [92, 93].

3.2. Anti-polyelectrolyte effect of zwitterionic polymer brushes

Zwitterionic polymers carry a total of neutral charge with equally balanced cationic and anionic groups, while traditional polyelectrolyte polymers always bear net charges. Due to ionic nature in both types of polymers, electrostatic interactions always play an important role in controlling their physicochemical properties. However, completely different from polyelectrolyte polymers, zwitterionic polymers shrink (collapse) in salt solution, but swell (expand) in water, and such unique behavior is called as 'anti-polyelectrolyte effect' (figure 6). Addition of salts in zwitterion polymers will screen out electrostatic interactions of intra- and inter-zwitterionic chains and break ionic pairs, thus causing the extension and dissociation of polymer chains. On the other hand, the extent of changes in chain conformations and associations for zwitterionic polymers strongly depends on charge distribution and identities [20, 56, 94]. SBMA and CBMA polymers present weak 'anti-polyelectrolyte effect' even in high salt concentrations (0.1–1 M) [95], while the later developed poly(3-(1-(4-vinylbenzyl)-1H-imidazol-3-ium-3-yl)propane-1-sulfonate) (polyVBIPS) exhibit strong 'anti-polyelectrolyte effect' in a dilute salt concentrations (0.05–0.1 M) due to its optimized spatial distribution of charged groups [21, 96]. Thus, the discovery and design of new zwitterionic polymers with the 'anti-polyelectrolyte effect' is still at its preliminary stage.

Due to this unique 'anti-polyelectrolyte effect' of zwitterionic polymers, Hong *et al* [96] developed salt-responsive polyVBIPS brushes, which could be switched reversibly and repeatedly between protein capture/release from undiluted blood plasma/serum in a controllable manner. On one hand, polyVBIPS brushes inducde protein adsorption by adopting a collapsed chain conformation in PBS solution; on the other hand, polyVBIPS brushes resisted protein adsorption from 100% blood plasma/serum once they adopt extended chain conformation treated with 1 M NaCl solution. The collapsed and extended chain conformation of polyVBIPS could be distinguished by film thickness differences by ~20 nm. Apart from proteins, polyVBIPS brush also showed its switching ability to promote and resist bacterial attachment in PBS and salt solutions. As compared to other smart surfaces, polyzwitterionic surfaces offer alternative but more promising platform that can be regenerated between bio-adhesion and antifouling properties, where the former property is favored for tissue scaffolds and dental implants requiring cell proliferation and implant osseointegration, while the latter one is liked by biosensors, bioanalytical and diagnostics devices. From the structural viewpoint, Xiao *et al* [21] further studied the 'anti-polyelectrolyte effect' of polyVBIPS polymers. By tuning carbon spacer length (CSL = 1, 3, and 4) between zwitterionic groups, different cationic groups (imidazolium, ammonium, and pyridinium), and salt concentrations and types, five polyzwitterionic brushes (polyVBIPS, polyDVBAPS, polySVBP, polyDVBAMS, and polyDVBABS) were prepared to show salt-responsive surface properties, including that surface wettability could be changed from a highly hydrophobic surface (~60°) to a highly hydrophilic surface (~9°). Meanwhile, interfacial friction can also be changed from ultrahigh friction ($\mu \approx 3.15$) to superior lubrication ($\mu \approx 10^{-3}$), and this is highly desirable for applications such as artificial joints (knees, hips, fingers) and eyes [56].

4. Multifunctional zwitterionic-based antifouling materials

4.1. Zwitterionic hydrogels with both antifouling and antibacterial properties

Hydrogels are considered as excellent biomimetic and biocompatible materials because their porous 3D network structures

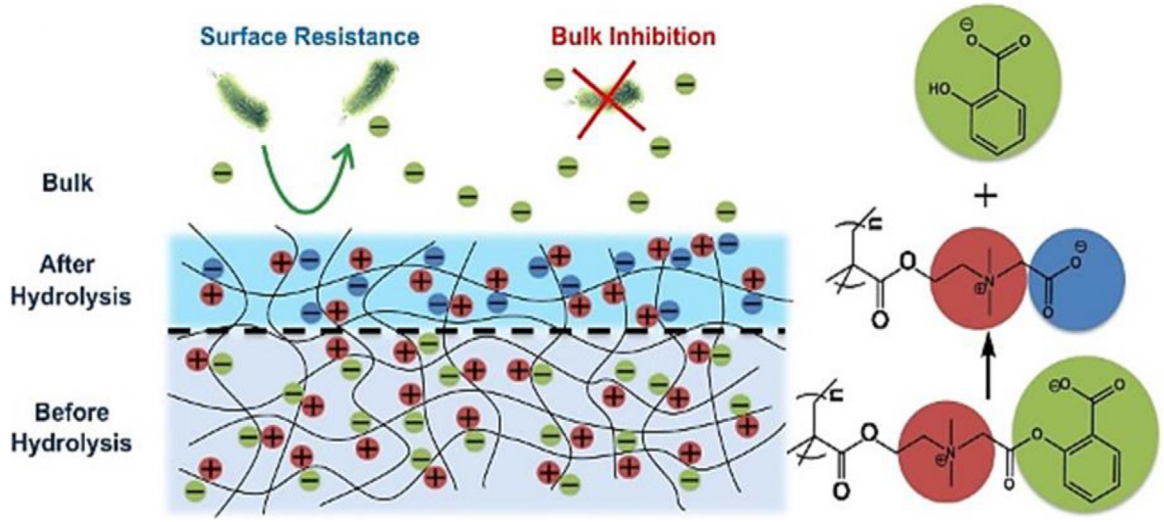

Figure 7. A hydrogel made up of the polyCBSA polymer (a designed zwitterionic polymer with cationic zwitterionic-precursor and an antimicrobial counter ion) able to keep the surface free from bacteria and inhibit bacterial growth in bulk simultaneously. Reprinted from [92], Copyright © 2012, with permission from Elsevier.

and high-water content (>80%) resemble many distinct structural and mechanical features of tissues and organs. However, most of hydrogels have been developed and used as tissue scaffolds, drug delivery devices, and artificial implants, all of which tend to promote the adhesion of proteins, cells, and tissue. Less efforts have been paid to reduce undesirable interactions between hydrogels and biomolecules, so challenging still remains for antifouling hydrogels. Historically, polyCBMA hydrogel was one of a few that have demonstrated their antifouling property. PolyCBMA hydrogels could reduce cell adhesion by 90% as compared to polyHEMA hydrogels [97]. When coating polyCBMA hydrogel on a glucose sensor tip, the sensor can retain not only its excellent detection ability for glucose, but also its stability in 100% human blood serum up to 12 d. Furthermore, zwitterionic polyCBMA hydrogels could be conjugated antimicrobial agent of salicylic acid (SA) via a hydrolyzable ester linkage to simultaneously achieve dual antifouling and antibacterial ability [92] (figure 7). Upon hydrolysis, SA was released from polyCBSA hydrogel network to inhibit bacterial growth on the surface and the surrounding solution. Meanwhile, hydrolysis transferred the SA group of CBSA to negatively charged carboxylate to maintain zwitterionic antifouling nature that makes surface highly resistant to bacterial attachment. Compared with hydrogel formed by polyCBMA alone or SA-incorporated polyCBMA, polyCBSA hydrogel synchronized both nonfouling and antimicrobial properties, which not only inhibited bacterial growth on the surface, but also kept bacteria from approaching the surface. Thus, combining both properties in materials and coatings provides a new and effective strategy to keep surfaces clean in a long term. Additionally, some components such as AgNPs [98] and chitosan [99] can also introduce additional antimicrobial activity in the zwitterionic-based hydrogels. Natural polysaccharide chitosan (CS) can form the first network of hydrogels, while antifouling zwitterionic sulfopropylbetaine (PDMAPS) and nonionic poly(2-hydroxyethyl acrylate) (PHEA) were chosen as the second and third network. The resultant hydrogels possessed high mechanical property (tensile stress 0.4 MPa, tensile strain ~10), high antimicrobial rates (91.6% to *S. aureus*, 89.7% to *E. coli*), and without any macrophage cell adhesion [99]. Accompanying the as mentioned excellent repellent to undesirable biomolecules interactions, zwitterionic hydrogels are quite appealing in applications like biosensor [100], contact lenses and cornea regeneration implants [48]. For example, by incorporating zwitterionic groups like SBMA with strong surface hydration ability enabled to achieve enhanced water content, optical transparency, and oxygen permeability (e.g. increase water content from 41.9% to 95.4%, optical transmittance from 2.3% to 98.1%, oxygen transmission from 17.5 to 54.7, which comparable to the commercial silicon contact lens) [48].

4.2. Zwitterionic nanoparticles with super stability

Nanoparticle-based drugs or diagnosis systems are very promising techniques for their high loading capacity, specific targeting, and intercellular uptake. However, one of major road blockers for drug delivery is unwanted nonspecific protein adsorption, which often result in nanoparticle aggregation and adverse response of immune system. Conventional PEGylation-coated nanoparticles are subject to rapid oxidation in the presence of oxygen and transition metal ions, thus losing antifouling property and the circulation of nanoparticles. Alternatively, coating of zwitterionic materials on nanoparticles may prevent the aggregation, precipitation, or clearance of nanoparticles, thus allowing them to increase circulation time *in vivo* and the chance for specific targeting via passive (e.g. a leaky vasculature) or active (e.g. antibodies or aptamers) pathways [101]. Yang *et al* [23] modified gold nanoparticles (GNPs) with polyCBMA whose activated carboxyl groups were further linked bio-recognition elements (anti-ALCAM) for detecting leukocyte cell. In sharp contrast to PEG-coated GNPs, polyCBMA-GNPs could well maintain their hydrodynamic diameters unchanged in 100% human

Figure 8. The polyCBAA-coated GNPs (polyCBAA-GNPs) immobilized with antibodies and the surfaces are highly resistant to nonspecific protein adsorption after antibody immobilization without agglomeration. Reprinted from [23], Copyright © 2009, with permission from Elsevier.

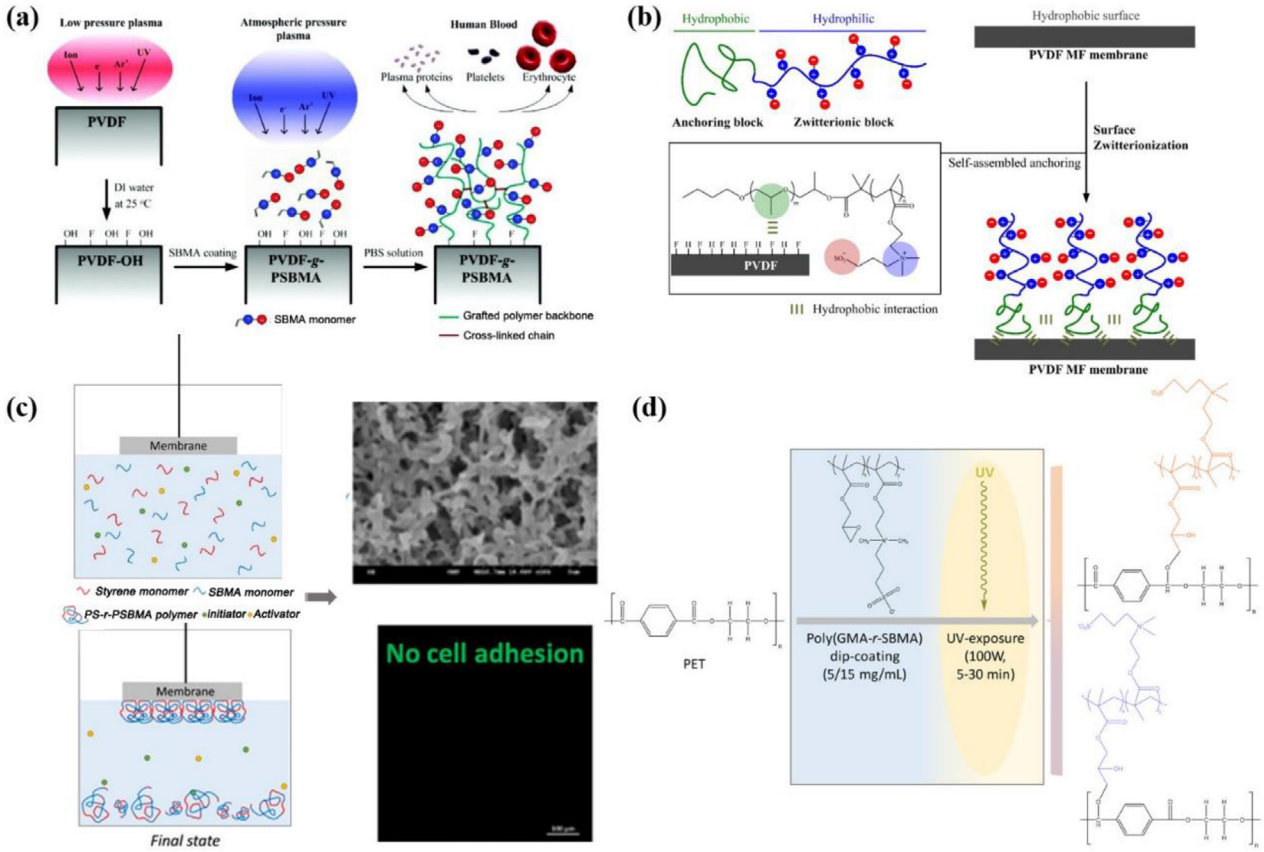

Figure 9. Surface resistance of zwitterionic antifouling membranes prepared by different surface coating methods to proteins, cells, and bacteria, (a) PVDF-*g*-pSBMA membrane by atmospheric plasma-induced surface copolymerization, (b) PPO-*b*-pSBMA-coated PVDF membrane by the self-assembling coating process of PPO-*b*-pSBMA copolymers on PVDF microfiltration membranes, (c) PS-*r*-pSBMA-coated PVDF membrane by a combination of polymerization and self-assembling process, (d) poly(GMA-r-SBMA)-functionalized PET membrane by self-assembly assisted dip-coating and UV irradiation. (a) Reprinted with permission from [85]. Copyright © (2008) American Chemical Society. (b) Reprinted from [109], Copyright © 2013, with permission from Elsevier. (c) Reprinted from [110], Copyright © 2018, with permission from Elsevier. (d) Reprinted with permission from [111]. Copyright © (2019) American Chemical Society.

blood serum solution up to 70 h, indicating that polyCBMA-GNPs are super stable in complex media without agglomeration. Super stability of polyCBMA-GNPs also enabled its ultralow fouling background to realize specific recognition of antigen by anti-ALCAM in 100% human blood serum (figure 8). Also, the designed zwitterionic dopamine sulfonate (ZDS) ligands were able to coat on superparamagnetic iron oxide nanoparticles (SPIONs) for stabled magnetic resonance imaging (MRI) [102]. Zwitterionic dopamine moiety in ZDS provided strong binding affinity to SPIONs, while the combination of quaternary amine and sulfonate group offers long-term pH stability in a range of 6.0–8.5. The resultant ZDS-SPIONs showed high stability not only in PBS or NaCl solution for a month, but also in fetal bovine serum without significant aggregation and size changes due to their high surface resistance to nonspecific protein adsorption.

4.3. Zwitterionic antifouling membranes

Protein-resistance is also an important feature of ultrafiltration membranes for biomedical applications including blood/protein separation and purification. Undesirable nonspecific protein adsorption on membrane surface or inside membrane pores will rapidly compromise the permeation flux, leading

to the failure of ultrafiltration function of membranes in very short time. A random sulfobetaine copolymer (DMMSA-BMA) synthesized by reacting hydrophilic N,N-dimethyl-N-methacryloxyethyl-N-(3-sulfopropyl) (DMMSA) with hydrophobic butyl methacrylate (BMA) through radical polymerization achieved excellent flux recovery property after blending with polyethersulfone (PES). At 8.0 wt% DMMSA-BMA concentration, the BSA flux of PES membrane can increase from ~40 to ~60 l $(m^2\ h)^{-1}$, consequently, irreversible fouling was considerably reduced, so that flux recovery ratio achieved as high as 82.8% after simple water flushing [103]. Later, an integrated plasma technique (figure 9(a)) was adopted to graft zwitterionic polySBMA layer onto different membranes such as poly(vinylidene fluoride) (PVDF) [104, 105], polypropylene (PP) [106], and poly(tetrafluoroethylene) (ePTFE) membranes [107]. Zwitterionic antifouling membranes can be designed by introducing poly-zwitterionic functionalized multiwalled carbon nanotubes (MWNT) as nanocomposites into the ultrafiltration polymer membrane. Adding 1 wt% polySBMA and poly(sulfone) (PSF) functionalized MWNT hybrid (MWNT-PSF/PSBMA) into PSF film led a significant reduction of fibrinogen protein adsorption to 7.2% as compared to the pristine PSF membrane [108].

However, surface grafting and polymerization methods are somehow too complicate to be applied to a large-scale production. To overcome this limit, some facile surface self-assembly processes are developed. First, as shown in figure 9(b), a simple dip-coating process was developed by incorporating diblock copolymer poly(propylene oxide)-block-poly(sulfobetaine methacrylate) (PPO-*b*-pSBMA) into PVDF membranes to achieve surface zwitterionization, and the presence of strong hydrophobic anchorage group from PPO allowed PPO-*b*-pSBMA to strongly interact with PVDF membranes. The resulting membranes achieved 15% of fibrinogen adsorption and 45% of protein adsorption from undiluted human plasma solution as compared with the virgin PVDF [109]. Furthermore, another simple one-step polymerization and membrane surface-modification was developed by self-depositing polystyrene (PS) and polySBMA onto PVDF membrane at the presence of azobisisobutyronitrile (AIBN) in 60 °C methanol solution (figure 9(c)). At optimal conditions of a 50/50 of SBMA/styrene monomer ratio and total 5 wt% SBMA and styrene in methanol solution, 5 h reaction time, the PS-*r*-pSBMA/PVDF membranes exhibited superior surface hydrophilicity (~0° water contact angle) and surface resistance to 90% of fibrinogen adsorption. The antifouling property of this optimized PS-*r*-pSBMA/PVDF membrane realized was nearly complete resistance to platelets, leukocytes, erythrocytes, whole blood and *E. coli* adhesion [110], superior to the former zwitterionization membranes like pSBMA/PVDF [104] and pSBMA/PP [106] prepared through complicated radical polymerization. A further combination of dip-coating process with UV irradiation enabled the covalent grafting of poly(glycidyl methacrylate-*r*-SBMA) onto poly(ethylene terephtalate) (PET) membrane and reduced bacterial attachment by 70%–80%, protein adsorption from whole blood by 80%, and fibroblast cell adhesion by 95%, without greatly altering the porosity of PET membranes [111] (figure 9(d)).

4.4. Zwitterionic wound dressings

Antifouling properties of zwitterionic polymers are critical for wound healing [46], because unwanted protein adsorption always causes collagenous capsules to inhibit wound closure. Development of highly nonfouling wound dressing, in combination with specific drugs or growth factors, has been considered as a promising strategy to treat skin wounds. An ABA triblock copolymer was developed and consisted of a thermo-responsive poly (N-isopropylacrylamide) (PNIPAM) as two outer A blocks and a positively-charged hydrolysable betaine ester loaded with an antimicrobial drug (salicylate) as an inner B block. The resultant ABA copolymers enabled to realize a rapid gelation of A blocks at body temperature, the controllable release of antimicrobial drugs from B blocks for inhibiting bacteria growth, and the hydrolysis of cationic betaine ester to its zwitterionic form for preventing bacterial adhesion [112] (figure 10(a)). Study of the ultra-low-fouling zwitterionic hydrogels (polyCBMA) had demonstrated that the gel could resist capsule formation for 3 months in mice, as compared to the commonly used polyHEMA hydrogels that was fully encapsulated by collagens after 4 weeks (figure 10(b)) [45]. In addition to zwitterionic polyCBAA wound dressing hydrogels alone, Ag nanoparticles (AgNPs) can also be encapsulated into polyCBAA hydrogels, which offered additional antibacterial ability to accelerate and realize a complete wound closure of *in vivo* murine model by 14 d (figure 10(c)) [113]. Furthermore, Wu *et al* [46] synthesized ultra-low-fouling zwitterionic polySBMA hydrogels and applied them to full-thickness cutaneous wounds in mice. They found that wounds treat with polySBMA hydrogels were almost scar-less after 17 d, in sharp contrast to large wound areas treated with pure PEG hydrogel. More importantly, the incorporation of SBMA into PEG hydrogels also enhanced the overall wound healing efficiency as compared to pure PEG hydrogels. PolySBMA hydrogel, due to their unique antifouling and mechanical properties, have demonstrated its ability to promote full-thickness excisional acute wound regeneration in mice by enhancing angiogenesis, decreasing inflammation response, and modulating macrophage polarization (figure 10(d)).

4.5. Zwitterionic antifouling elastomers

Elastomers have huge demands in biomedical and industrial applications. Most of elastomers, particularly polydimethylsiloxane (PDMS) elastomer, are highly hydrophobic [114], which greatly limits their antifouling applications. Use of zwitterionic polyCBMA to modify PDMS surface via the surface-initiated ATRP method enabled to form a super hydrophilic polyCBMA layer [115]. Strong chain–chain interactions of polyCBMA lead to the electrostatically-induced hydration and suppressed the PDMS surface reconstruction. The zwitterionic polymer modified PDMS elastomer is highly stable in

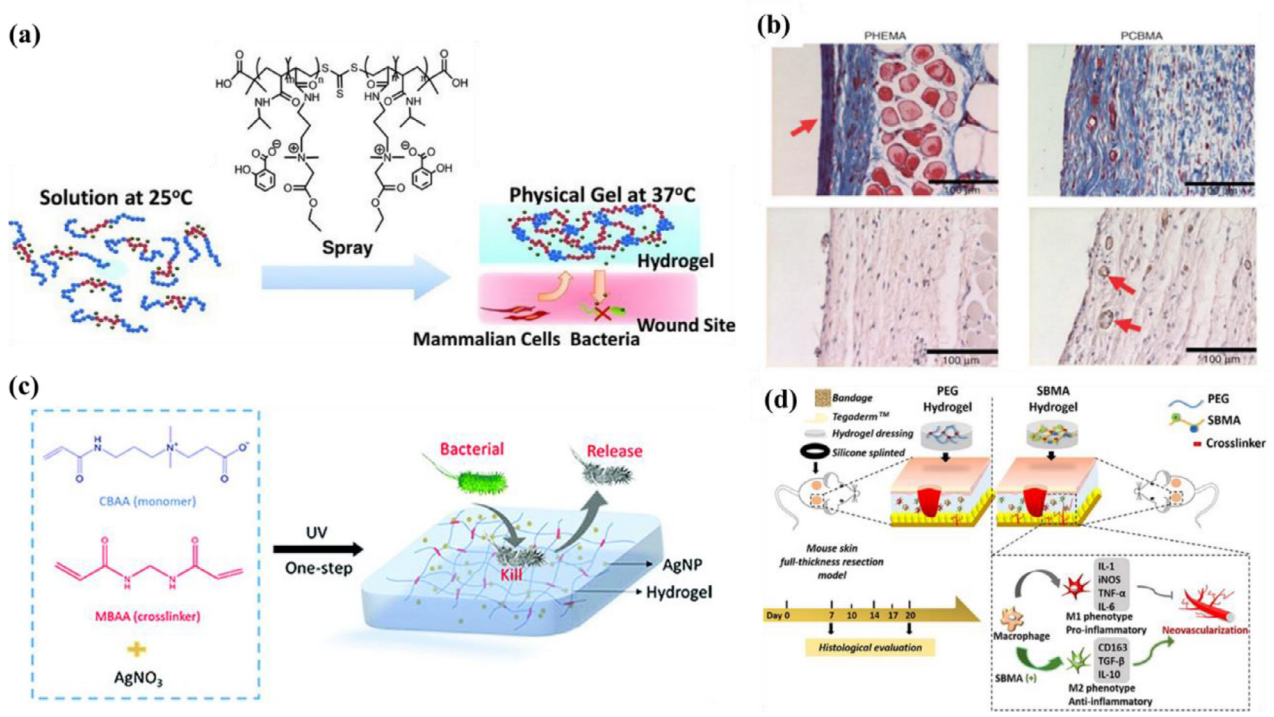

Figure 10. Zwitterionic polymer hydrogels for wound dressing. (a) PNIPAM-polyCB-PNIPAM wound dressing with both antifouling and antibacterial capacity, (b) polyCBMA wound dressings for promoting collagen (blue staining) and blood vessel (brown staining) formation in tissues, as compared to polyHEMA wound dressings, (c) polyCB-AgNPs wound dressing to prevent fouling and treat bacterial infection, and (d) polySBMA wound dressing for accelerating wound regeneration in full-thickness cutaneous wounds in mice, as compared to PEG hydrogel dressing. (a) [112] John Wiley & Sons. Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) [45] © 2013 Nature America, Inc. All rights reserved. With permission of Springer. (c) Reproduced from [113] with permission of The Royal Society of Chemistry. (d) Reprinted from [46], Copyright © 2018, with permission of Elsevier.

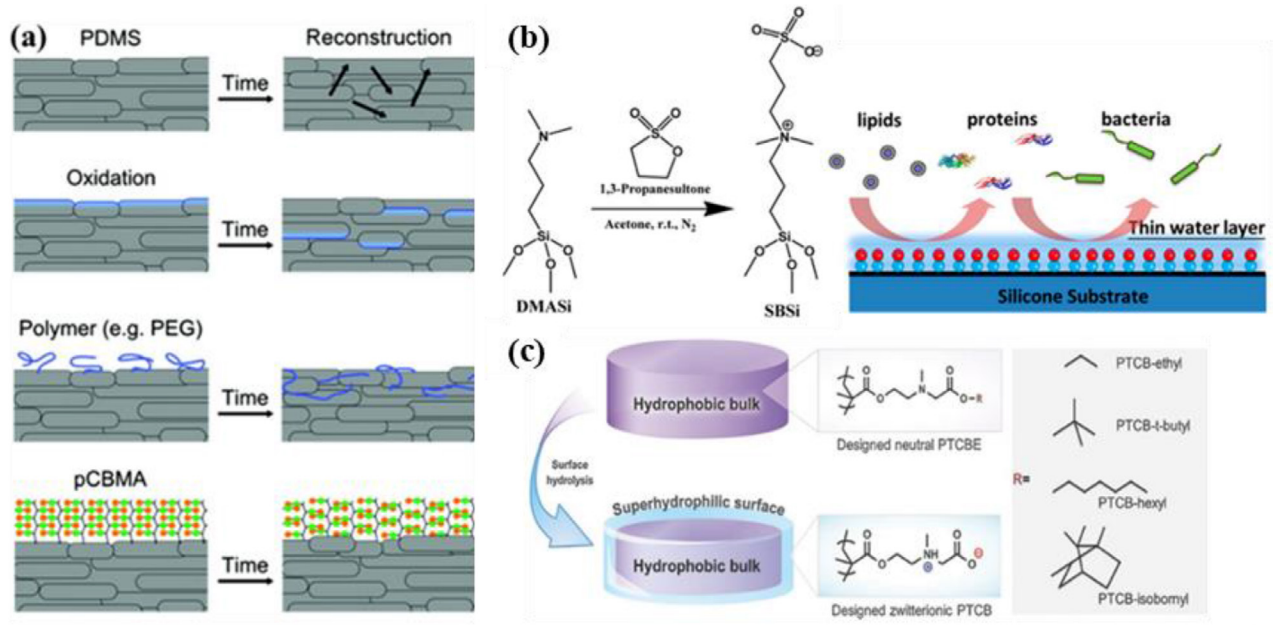

Figure 11. Zwitterionic antifouling elastomers. (a) PolyCBMA-coated PDMS surface to resist protein adsorption up to 74 d, (b) SBSi-coated PDMS elastomer to resist nonspecific adsorption of bacteria, proteins, and lipids, and (c) hydrolyzed carboxybetaine ester polymer (PTCBE) to resist protein adsorption. (a) Reprinted with permission from [115]. Copyright © (2012) American Chemical Society. (b) Reprinted with permission from [116]. Copyright © (2014) American Chemical Society. (c) [117] John Wiley & Sons. Copyright © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

wet condition, with <2% protein adsorption after 74 d (figure 11(a)). Yeh *et al* [116] further developed a hybrid zwitterionic-PDMS elastomer by covalently silanizing the sulfobetaine silane (SBSi) on PDMS elastomer. The resulting SBSi-PDMS elastomer reduced almost ~96% of bacterial adhesion as compared to unmodified PDMS ones (figure 11(b)). More recently,

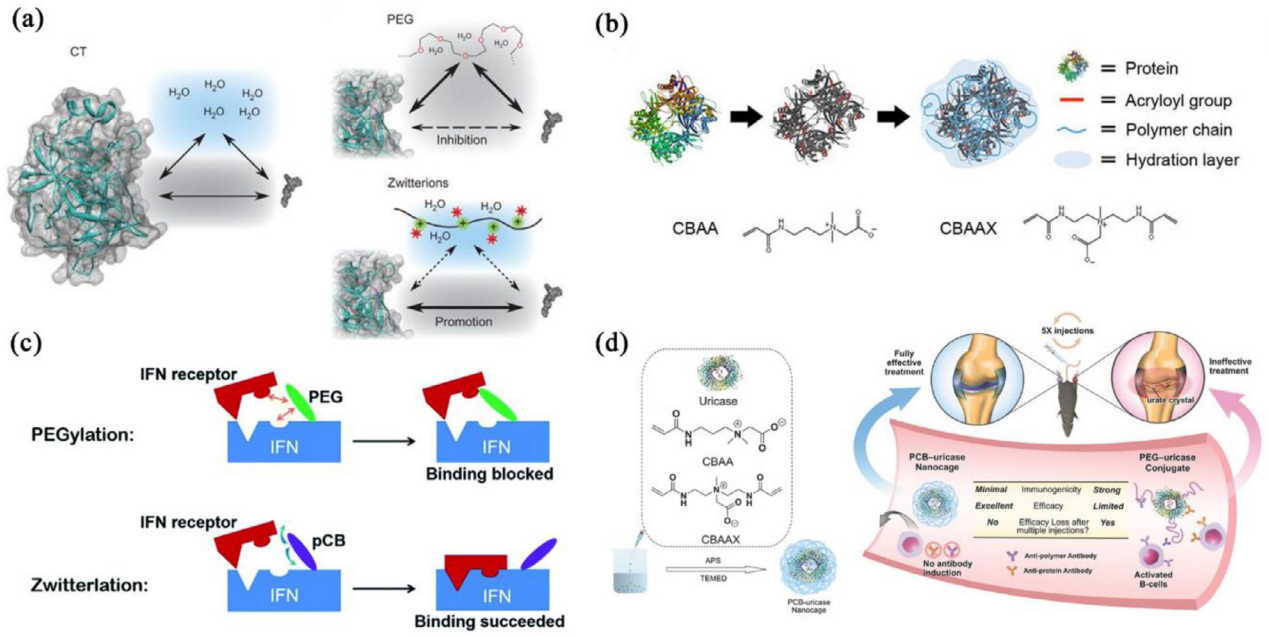

Figure 12. Zwitterionic polymer-coated proteins. (a) Zwitterionic polymer-induced interacial interactions between proteins and substrate, (b) zwitterionic protein encapsulation: the process of zwitterionic polyCBAA network encapsulation of a protein surface and the consequently formation of hydration layer. (c) A zwitterionic polyCB-conjugated IFN-α2a to reduce the bioactivity loss of IFN-SO3SO32a, (d) polyCB nanocages for uricase encapsulation to minimize the production of antipolymer or antiuricase antibodies and to improve pharmacokinetics for gout treatment. (a) [120] © Macmillan Publishers Ltd. All rights reserved. With permission of Springer. (b) Reproduced from [121]. (c) Reproduced from [123]. CC BY 3.0. (d) [44] John Wiley & Sons. Copyright © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

a coating-free antifouling zwitterionic-based elastomer was developed by replacing the quaternary amines in zwitterionic poly(carboxybetaine) (polyCB) moiety with tertiary amines and further protecting its carboxyl groups with esters [117]. In this way, a superhydrophilic and zwitterionic polyCB can be converted into charge-neutral and hydrophobic a tertiary carboxybetaine ester polymer (PTCBE). The resulting PTCBE exhibited high hydrophobicity to repel water in bulk, but upon hydrolysis PTCBE was converted into polyCB that exhibited zwitterionic characteristics and excellent nonfouling properties. The hydrolyzed, hydrophilic polyCB layer can resist 95% of protein adsorptions (figure 11(c)). This design strategy offers a new and simple hydrolysis to develop coating-free, antifouling elastomers without sacrificing its bulk mechanical properties.

More challenging antifouling property is required in elastomers for blood contacting device. In this case, elastomers with maintained thromboresistance during degradation is highly desirable, and can hardly achieved by simple surface modification or grafting approaches. To this end, elastomers with zwitterion incorporated backbone can be an effective solution. For example, biodegradable polyurethanes were designed and synthesized with zwitterions (SB and CB) incorporated into the polymer backbone [118, 119]. As a result, the incorporation of zwitterions could achieve tunable surface and mechanical properties, and maintain nonthrombogenic properties after periods of degradation. The polyurethane showed scattered platelet aggregates and deposition after 2 weeks, while it was hard to find any platelets on the polyester SB urethane ureas surfaces which already had been partially degraded over 2 months.

4.6. Zwitterionic-coated proteins

Unlike PEGylated protein therapeutics products that inevitably introduce additional immune response via haptenic effect, zwitterionic polymers could be coated on proteins to improve their stability and immunological properties [120–122]. Generally speaking, hydrophobic interactions are critical for protein and substrate binding (or bioactivity). Different from the PEGylation that could reduce such hydrophobic interaction at protein-substrate interface due to its amphiphilicity [50], super-hydrophilicity of zwitterionic polymers can greatly draw away water from the hydrophobic regions of the protein, increase the hydrophobic–hydrophobic driving force of the substrate and binding site, and allow them to interact consequently. An early study of polyCB and chymotrypsin (CT) conjugation showed that zwitterionization not only preserved enzyme bioactivity, but also slightly increased its binding affinity to peptide substrates, in contrast to PEGylation-induced the binding affinity decreases of enzymes [120] (figure 12(a)). Furthermore, zwitterionic polyCB-based hydrogel was coated on protein surface to form a core–shell structure. The resultant polyCB-encapsulated uricase displayed high thermal stability to retain 100% activity at 65 °C and prolonged circulation up to 3.6-fold improvement over uricase-PEG, without any detectable anti-protein and anti-polyCB antibodies [121] (figure 12(b)). Zwitterionic polymer-conjugated proteins also significantly mitigated the bioactivity loss of interferon alpha-2a (IFN-α2a). polyCB-conjugated IFN-α2a exhibited 62.1% antiproliferative activity that was 4.4-fold higher than that of the PEGylated IFN-α2a (14.2%), as well as prolonged blood

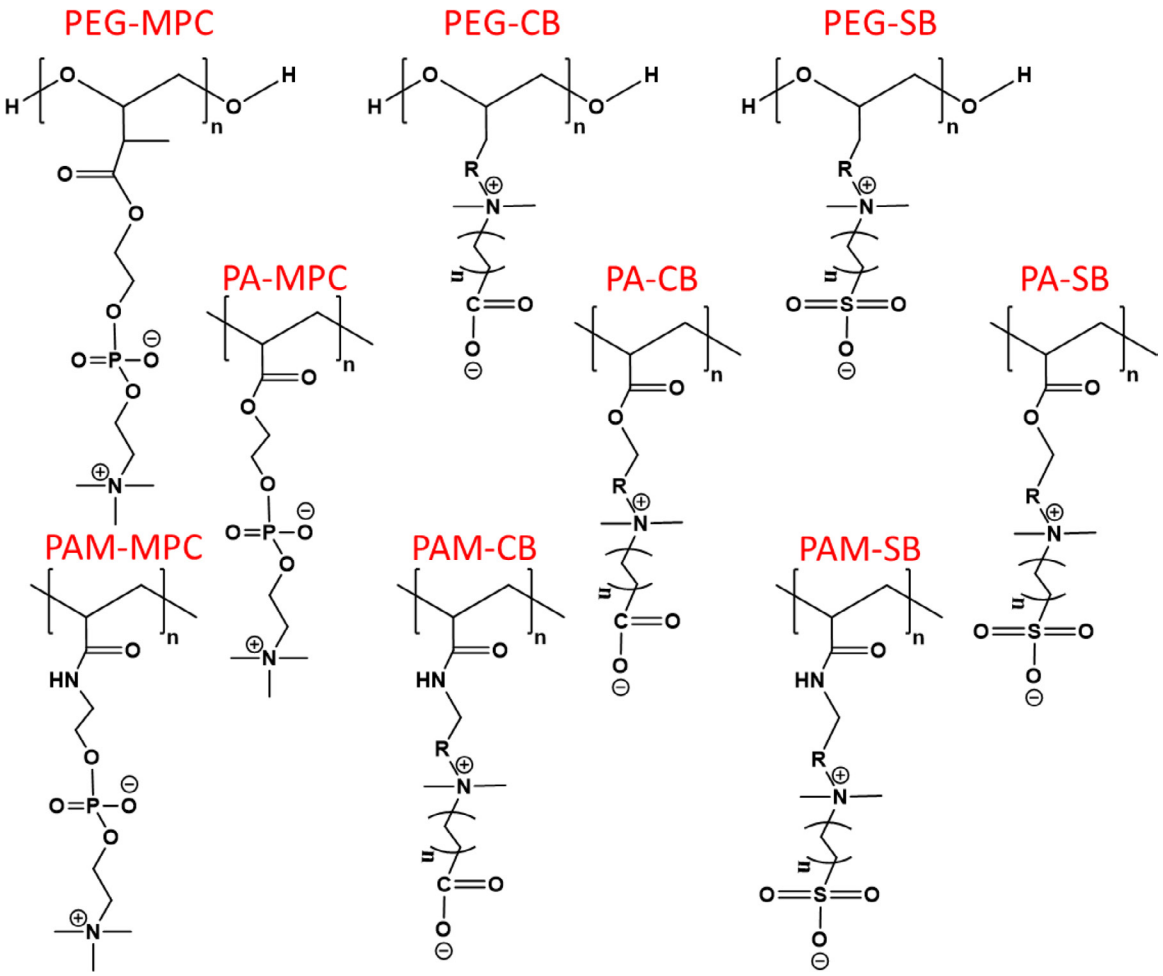

Figure 13. Design of hybrid hydrophilic-zwitterionic polymers for superior long-term fouling resistance stability.

circulation [123] (figure 12(c)). Another example was a polyCB-based nanocage that was recently developed to minimize the influence of the encapsulation on enzymatic activity [44]. Zwitterionic polyCB polymers can physically wrap therapeutic proteins and protect proteins noninvasively as a nanocage. High hydrophilicity and bio-inertness of zwitterionic polyCB make the nanocage effectively eradicate almost all immune responses, without evoking any loss of efficacy in clinical-mimicking gouty rat model (figure 12(d)).

5. Conclusions and perspectives

Throughout decade research, zwitterionic materials have attracted the growing interest as excellent antifouling materials for their promising applications in diverse fields. Significant progress has been achieved in the design and synthesis of different zwitterionic materials, whose antifouling properties have been well optimized for promoting other important functions both *in vitro* and *in vivo* for biosensors, targeting drug/gene delivery, wound dressing, contact lenses, separation membrane, and therapeutic applications. Despite the great success so far, the research in zwitterionic materials is still in its early stage as compared to PEGylated materials. There are still some remaining challenges to be overcome before the widespread practical applications of zwitterionic materials become possible. Here, we offer some personal perspectives regarding challenges and future research for zwitterionic materials.

First of all, the most prominent issue with antifouling materials (not limited only to zwitterionic materials) is still their short-term structural stability against different biofoulants in much longer timescale. While zwitterionic materials have been well demonstrated for their superior antifouling properties in simple aqueous solution and complex media (e.g. undiluted human blood, cultured cells and bacteria) for a short period time (hours to weeks), they are still lacking sufficient quality or long-term stability, presumably the degradation of zwitterionic groups (e.g. sulfonium groups are rapidly degraded by the attack of nucleophiles in a natural environment). Thus, modification of zwitterionic polymer backbone with protection agents is alternative strategy to remedy the long-term stability issue. Nowadays, PEG, polyacrylamide, and polyacrylate are among the most popular antifouling materials. It is, therefore, not a surprising to copolymerize highly hydrophilic groups (e.g. ethylene glycol, amide, and ester group) with zwitterionic groups (e.g. CB, SB, MPC) to produce hybrid hydrophilic-zwitterionic polymers (figure 13). For example, polyacrylamides and

poly(vinyl amides) usually contain tertiary amide moiety that will simultaneously increases the resistance to hydrolysis. Hydrophobic polystyrenes and poly(vinyl pyridines) are chemically very stable, and could be integrated with zwitterionic polymers to enhance the long-term stability of hybrid hydrophobic-zwitterionic polymers at the expense of antifouling behavior to a reasonable level. So, combination of hydrophilic/hydrophobic and zwitterionic moieties into a single polymer chain allows us to not only introduce additional hydration forces (e.g. hydrogen bonding) to enhance antifouling stability, but also increase the structural/chemical diversity of zwitterionic polymers.

From a computational viewpoint, very few molecular simulations have been carried out to study the interfacial properties of zwitterionic polymers. Current MD simulations largely focus on bulk zwitterionic polymers and their interactions with and without proteins, but not on zwitterionic polymer brushes that are anchored on the substrate to mimic antifouling surface. MD simulations of zwitterionic polymer brushes require not only more accurate force fields to describe surface potential energy, but also optimal lattice structures to better determine polymer packing structures and density. Thus, no MD simulation studies have been reported so far to directly study the protein adsorption/resistance on zwitterionic polymer brushes. If workable, such interfacial MD simulations enable to directly examine the effects of polymer thickness and grafting density on interfacial interactions between zwitterionic polymer brushes and a protein in the presence of water and counter ions, as well as to offer atomic details of hydration-induced structural and energy barriers at the protein-brush interface for better understanding antifouling mechanisms. We are currently simulating zwitterionic polymer brushes in the absence and presence of proteins. More importantly, different from bulk polymer systems with relatively well-controlled properties, zwitterionic polymer brushes and coatings often contains heterogeneous data (e.g. physicochemical, morphological, and antifouling properties) obtained from different labs and at different conditions. Some datasets may contain erroneous or inconsistent entries. Thus, it is equally important to (1) collect a reliable benchmarking dataset and (2) develop a computational predictive model for better assessing the component-structure-property-performance relationship of zwitterionic polymer coatings and for achieving the structural-based design of next-generation zwitterionic materials with optimal properties and desirable functions.

Acknowledgment

J Z thanks financial supports from NSF (DMR-1806138. Y C thanks financial supports from Ministry of Science and Technology (MOST 106-2628-E-033 -001-MY3).

ORCID iDs

Jie Zheng https://orcid.org/0000-0003-1547-3612

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