

Self-healing Hydrogels and Underlying Reversible Intermolecular Interactions

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Abstract Self-healing hydrogels have attracted growing attention over the past decade due to their biomimetic structure, biocompatibility, as well as enhanced lifespan and reliability, thereby have been widely used in various biomedical, electrical and environmental engineering applications. This feature article has reviewed our recent progress in self-healing hydrogels derived from mussel-inspired interactions, multiple hydrogen-bonding functional groups such as 2-ureido-4[1H]-pyrimidinone (UPy), dynamic covalent bonds (e.g., Schiff base reactions and boronic ester bonds). The underlying molecular basics of these interactions, hydrogel preparation principles, and corresponding performances and applications are introduced. The underlying reversible intermolecular interaction mechanisms in these hydrogels were investigated using nanomechanical techniques such as surface forces apparatus (SFA) and atomic force microscopy (AFM), providing fundamental insights into the self-healing mechanisms of the hydrogels. The remaining challenging issues and perspectives in this rapidly developing research area are also discussed.

Keywords Self-healing hydrogels; Mussel-inspired Interaction; Multiple hydrogen-bonding; Dynamic covalent bonds; Intermolecular forces

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INTRODUCTION

Hydrogels are water-swollen polymeric materials that maintain a distinct three-dimensional (3D) structure.^[1–3] They have been widely used in biomedical applications including drug delivery, tissue engineering and wound healing owing to their high resemblance with biological tissues and extracellular matrices (ECM) by sharing common natures of water-abundant, soft and highly porous structures.^[3–16] Also, hydrogels with some advanced features like conductivity and stretchability can serve as ideal candidates for soft electronics such as implantable bioelectronics, wearable sensory devices, artificial electronic skins, flexible touch panels, actuators and triboelectric generators.^[17–26] In addition, the 3D network, porous structure and high water retention of hydrogels make them promising in environmental applications like wastewater treatment.^[27–31]

Self-healing generally refers to a material's capability to spontaneously heal or mend fractures and defects, restoring their structures and functionalities after inflicted damage.^[32–34] Self-healing hydrogels have attracted considerable attention over the past decade. With self-healing ability, the lifetime of hydrogels can be greatly extended, and their reliability and durability can be enhanced. Different from conventional hydrogels that are cross-linked by permanent covalent

bonds, self-healing hydrogels are generally constructed by introducing reversible physical bonds (e.g., hydrogen bonding, electrostatic forces, hydrophobic interactions, metal-ligand coordination and host-guest interactions) or dynamic covalent chemistries (e.g., Schiff base or imines, boronate complexations, hydrazones, disulfide bonds) as crosslinks, as shown in Fig. 1.^[33–38] The reversible and dynamic breakage and reconfiguration of these bonds enable the hydrogels to reform networks and restore structures after damage. Besides self-repairing property, the introduction of various reversible interactions can also endow the hydrogels with diverse functionalities such as injectability, stimuli responsiveness and strain-stiffening property to better fulfill the increasing demands of advanced and multifunctional modern materials.

On the other hand, since reversible molecular interactions play critical roles in the construction of hydrogel networks and their self-healing performances, it is of great significance to characterize these intermolecular interactions quantitatively, which provides a fundamental understanding on the gelation and self-healing mechanisms as well as inspires future design of novel self-mending materials. Nanomechanical tools such as surface forces apparatus (SFA) and atomic force microscopy (AFM) are powerful techniques for quantitative characterizations of the intermolecular and surface interaction forces at the molecular level or nano scale. SFA is one of the most sensitive and widely used techniques for quantifying the physical forces (e.g., van der Waals, electrical double layer, hydrophobic, hydration, metal ion coordination, and

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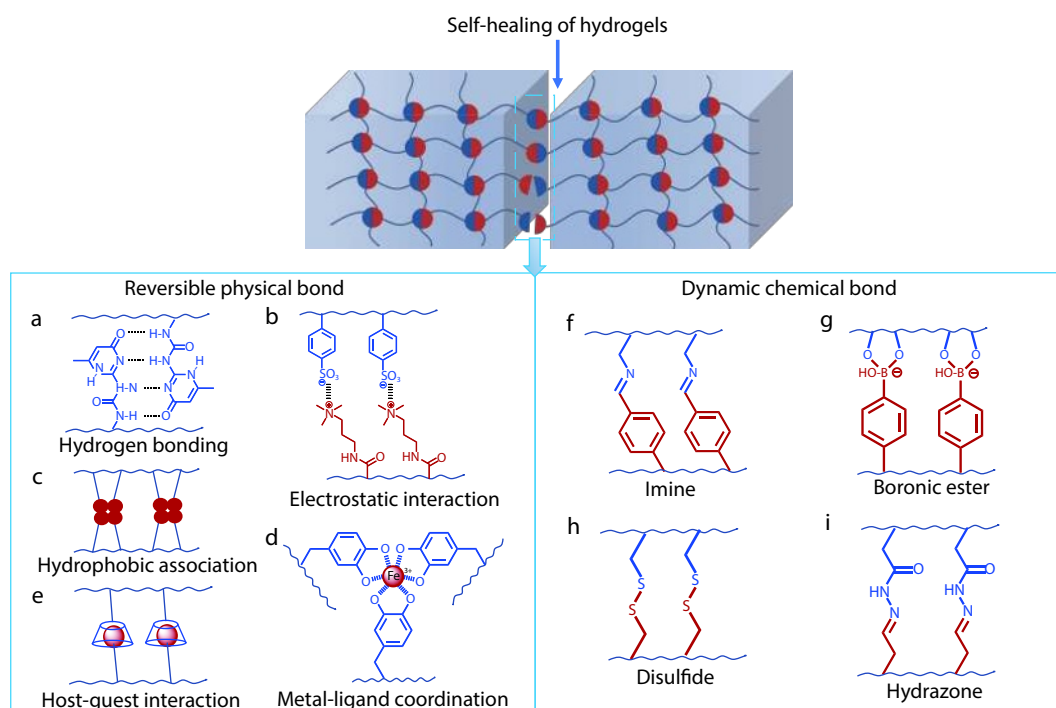


Fig. 1 Different strategies for the construction of self-healing hydrogel networks based on (a–e) reversible physical interactions and (f–i) dynamic covalent bonds.

ligand-receptor interactions) between opposing surfaces in vapors or complex fluids as a function of their absolute separation distance, with a force sensitivity of <10 nN and an absolute distance resolution of <0.1 nm.^[39–47] AFM can measure forces between a sharp nano tip (or a solid colloidal particle, gas bubble or emulsion drop) and a substrate surface, generally with a force sensitivity of $10–100$ pN.^[48–57] By employing SFA, AFM and other tools, the interaction forces among the different components in hydrogel systems can be facily quantified from the molecular level to nano-/micro-scale.

In this feature article, our recent progress in developing self-healing hydrogels has been reviewed, mainly focusing on hydrogels formed by four types of interactions, *i.e.*, mussel-inspired molecular bindings, multiple hydrogen-bonding interaction *via* 2-ureido-4[1*H*]-pyrimidinone (UPy) groups, Schiff base and boronic ester bonds. Our recent progress on characterizing these interactions using nanomechanical tools such as SFA and AFM has also been discussed, which provides useful insights into the gelation, self-healing, and stimuli-responsive mechanisms of hydrogels. Some related studies by other research groups are also reviewed to provide an overview of this field. The remaining challenges and future perspectives in this emerging and rapidly growing area are discussed.

MUSSEL-INSPIRED HYDROGELS

Marine mussels can hold fast to various surfaces including rocks, metals and organisms by secreting adhesive proteins that would form byssal thread and plaque to adhere to the substrates in complex seawater.^[58–61] Byssal threads can self-heal from injuries.^[62] The remarkable underwater adhesive capability and self-healing property of byssus are mainly attributed to a catecholic amino acid called 3,4-dihydroxyphenyl-L-

alanine (Dopa) which is able to participate in the formation of various interactions including oxidative covalent bonding (*e.g.*, quinone coupling and Michael addition) and reversible physical bonds (*e.g.*, hydrogen bonding, metal-catechol coordination, cation- π interaction, anion- π and π - π aromatic interaction), as displayed in Fig. 2(a).^[44,46,63–72] Inspired by the impressive adhesive and self-healing behaviors of mussels, dopamine or 3,4-dihydroxyphenethylamine, derived from Dopa, has been widely used as a molecular anchor in the fabrication of adhesive hydrogels,^[73–75] self-healing hydrogels,^[76–78] hydrogel coatings^[79–81] and so forth.

For the preparation of mussel-inspired hydrogels possessing self-healing behavior, it is critical to create reversible non-covalent crosslinks in hydrogel networks. Hydrogels based on coordination between Fe ions and catechol ligands have been extensively studied since the hardness, extensibility and self-healing of the cuticle of mussel byssal threads were correlated with the catechol-Fe³⁺ complexation.^[46] For instance, Messersmith and coworkers developed a self-healing hydrogel based on catechol-Fe³⁺ interpolymer cross-linking between DOPA-terminated 4-arm poly(ethylene glycol) (PEG) and ferric ions in FeCl₃ solution.^[77] The hydrogel demonstrated pH-mediated gelation behavior, *i.e.*, being a fluid at acidic condition (pH \sim 5), forming a sticky gel at pH \sim 8 and turning into an elastomeric gel at basic pH of 12, which was attributed to the stoichiometric transitions of the catechol-Fe³⁺ complexes at different pH values (monospecies at pH $<$ 5.6, bis- at 5.6 $<$ pH $<$ 9.1, and tris- at pH $>$ 9.1). Upon failure induced by shear strain or tearing, the tris-catechol-Fe³⁺ cross-linked gel could recover its storage modulus (*G'*) and cohesiveness within minutes. By replacing FeCl₃ solution to iron oxide nanoparticles (Fe₃O₄ NPs) dispersion during gel preparation, a more solid-like hydrogel was fabricated *via* reversible metal-coordination bonds at Fe₃O₄ NP surfaces.^[82] The gel

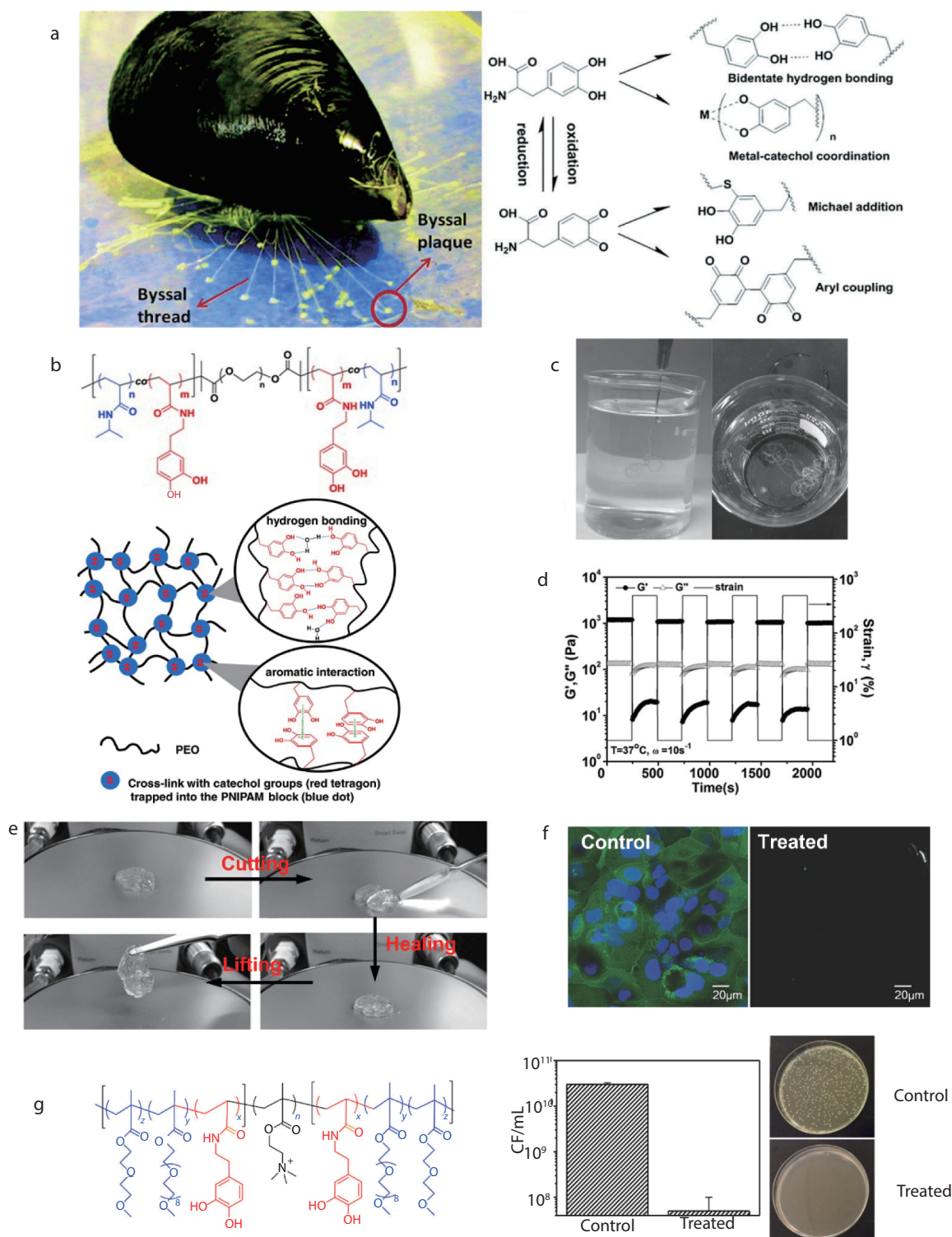


Fig. 2 (a) A mussel (*M. edulis*) attached to mica surface through byssal thread and byssal plaque, and schematic illustration of the various interactions (e.g., bidentate hydrogen bonding, metal-catechol coordination, Michael addition and acryl coupling) involved with DOPA and dopaquinone in the formation of mussel-inspired hydrogels. (Reproduced with permission from Ref. [63]; Copyright (2014) The Royal Society of Chemistry). (b) The mussel-inspired hydrogel based on self-assembly of an ABA triblock copolymer through bidentate hydrogen bonding and aromatic interactions between catechol moieties, showing (c) injectability, (d, e) self-healing capability and (f) anti-biofouling property. (Reproduced with permission from Ref. [76]; Copyright (2015) John Wiley & Sons). (g) The hydrogel formed by catechol-functionalized cationic ABA triblock copolymer and the demonstration of its antibacterial property. (Reproduced with permission from Ref. [78]; Copyright (2017) American Chemical Society).

displayed slower network relaxation upon shear strain and comparable self-healing performance.

The self-healing of mussel-inspired hydrogels can also be achieved through metal-free approaches. In a previous work, we reported a new type of mussel-inspired hydrogels based on self-assembly of ABA triblock copolymers through bidentate hydrogen bonding and aromatic interactions between catechol moieties.^[76] The A blocks of the copolymer are composed of catechol-functionalized thermo-sensitive poly(*N*-isopropylacrylamide) (PNIPAM) and the B block is hydrophilic PEG, as shown in Fig. 2(b). The copolymer solution is a free-flow viscous liquid at a lower temperature (*i.e.*, 4 °C). When warmed to room temperature, a 3D network is constructed *via* the association of dehydrated A blocks into micellar cores that are bridged by the hydrophilic B segments (Fig. 2b), resulting in the formation of a free-standing gel. The thermo-triggered sol-to-gel transition of the hydrogel is fast and completely reversible. This design endows the hydrogel with excellent injectability (Fig. 2c), which makes it promising for biomedical applications like drug delivery because of the non-invasive administration and ease of operation. More importantly, the hydrophobic PNIPAM domains protect the entrapped catechol moieties from environmental oxidation that would lead to irreversible quinone cross-linking and further loss of self-healing capability. The reversible interactions between catechol groups, *i.e.*, bidentate hydrogen bonding and aromatic interactions (quadrupolar and π - π stacking interactions), enable the hydrogel to completely heal from repeated damages induced by shear strain and cutting, as shown in Figs. 2(d) and 2(e), respectively. In addition, the hydrogel demonstrated exceptional antifouling performance

against nonspecific cell attachment owing to the non-fouling nature of PEG and inherent structure of the whole hydrogel (Fig. 2f). The anti-biofouling property is desired for biomedical applications because it could eliminate the adhesion of proteins or microorganisms to implanted hydrogels and possible inflammatory responses. Compared with self-healing hydrogels cross-linked through catechol-metal coordination that may pose risk to cells because of metal ions, this hydrogel *via* metal-free dopamine interactions with reduced cytotoxicity and enhanced transparency exhibits great potential in various biomedical applications. By engineering the molecular structure of the ABA triblock copolymer, the properties of the hydrogels can be further tuned to fulfill the demands of different applications. Another hydrogel was fabricated following a similar principle by employing catechol functionalized thermo-responsive PEG as A block and poly[2(methacryloyloxy) ethyl trimethylammonium iodide] (PMETA) as B block (Fig. 2g).^[78] Besides injectability, thermo-responsiveness, self-healing and antifouling properties, the hydrogel also shows good antimicrobial capability, *i.e.*, effectively inhibiting the growth of *E. coli* with a killing efficiency higher than 99.8%, due to the presence of cationic quaternary amine. The combination of multiple desirable functionalities makes the hydrogel an ideal candidate for a wide range of bioengineering applications like wound healing and drug delivery.

As aforementioned, the adhesion and cohesion of mussel byssal threads have inspired the development of numerous adhesives and/or self-healing materials based on mussel-inspired DOPA-mediated interactions. To understand the mechanisms of the outstanding adhesion and cohesion capabilities of byssus, nanomechanical force measurement tool, SFA,

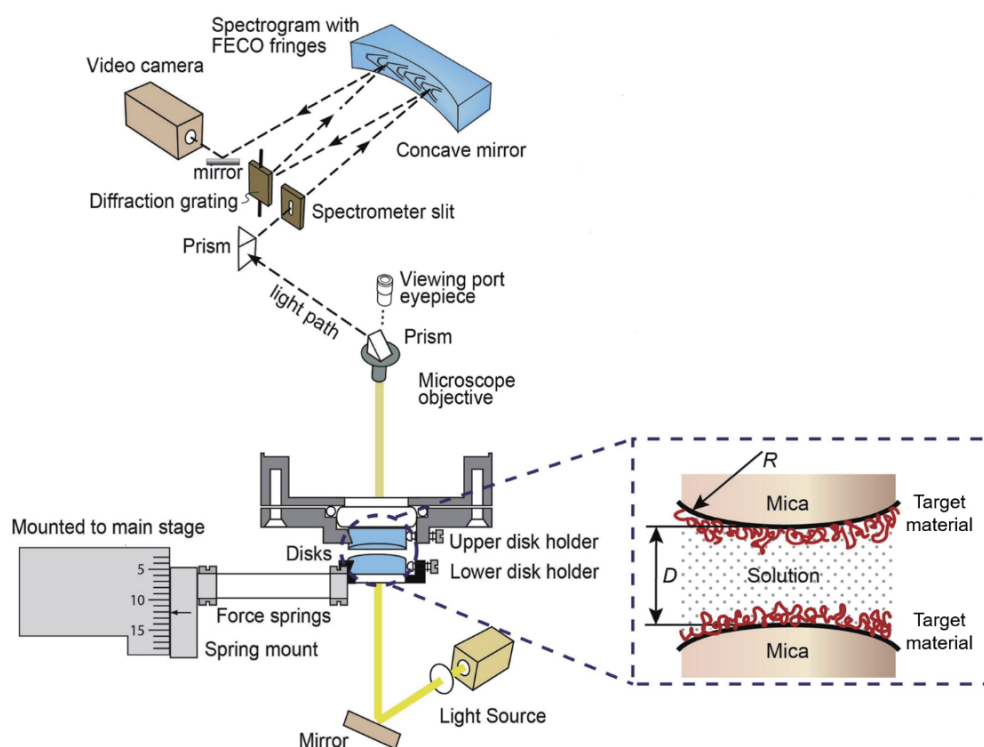


Fig. 3 Schematic illustration of typical SFA experimental setup for measuring the interaction forces between two surfaces in vapors or solutions. (Reproduced with permission from Ref. [44]; Copyright (2015) Elsevier).

plays an important role and has been widely applied in related research to characterize the molecular interactions. Fig. 3 shows the schematic of a typical SFA experiment setup for measuring the normal forces between two surfaces. In a typical SFA experiment, two back-silvered mica surfaces are glued onto two cylindrical silica disks (radius $R \sim 2$ cm), respectively. Targeted materials are coated on the mica surfaces which are then mounted into the SFA chamber in cross-cylinder configuration, the interaction of which is equivalent to a sphere of the same radius interacting with a flat substrate based on the Derjaguin approximation when their separation is much less than the radius. The amount of the targeted material coated on the mica surfaces may vary for different materials and coating strategies. For SFA measurements, a coating layer with high molecular coverage and low

surface roughness (generally less than several nanometers) is highly desired. Targeted materials can also be directly injected between the two surfaces. By bringing the two surfaces closer and into contact followed by separation, the normal interaction force $F(D)$ can be measured as a function of absolute surface separation distance D in real time. The forces are determined using the Hooke's law by measuring the bending of a force spring that the lower surface was mounted on and the distances between the surfaces are determined using an optical technique called multiple beam interferometry by employing fringes of equal chromatic order (FECO).^[45,83]

SFA has been employed for probing the interaction mechanisms of mussel foot proteins to various substrates and between mussel foot proteins themselves. In a previous work, we quantified the reversible DOPA-Fe³⁺ complexation inter-

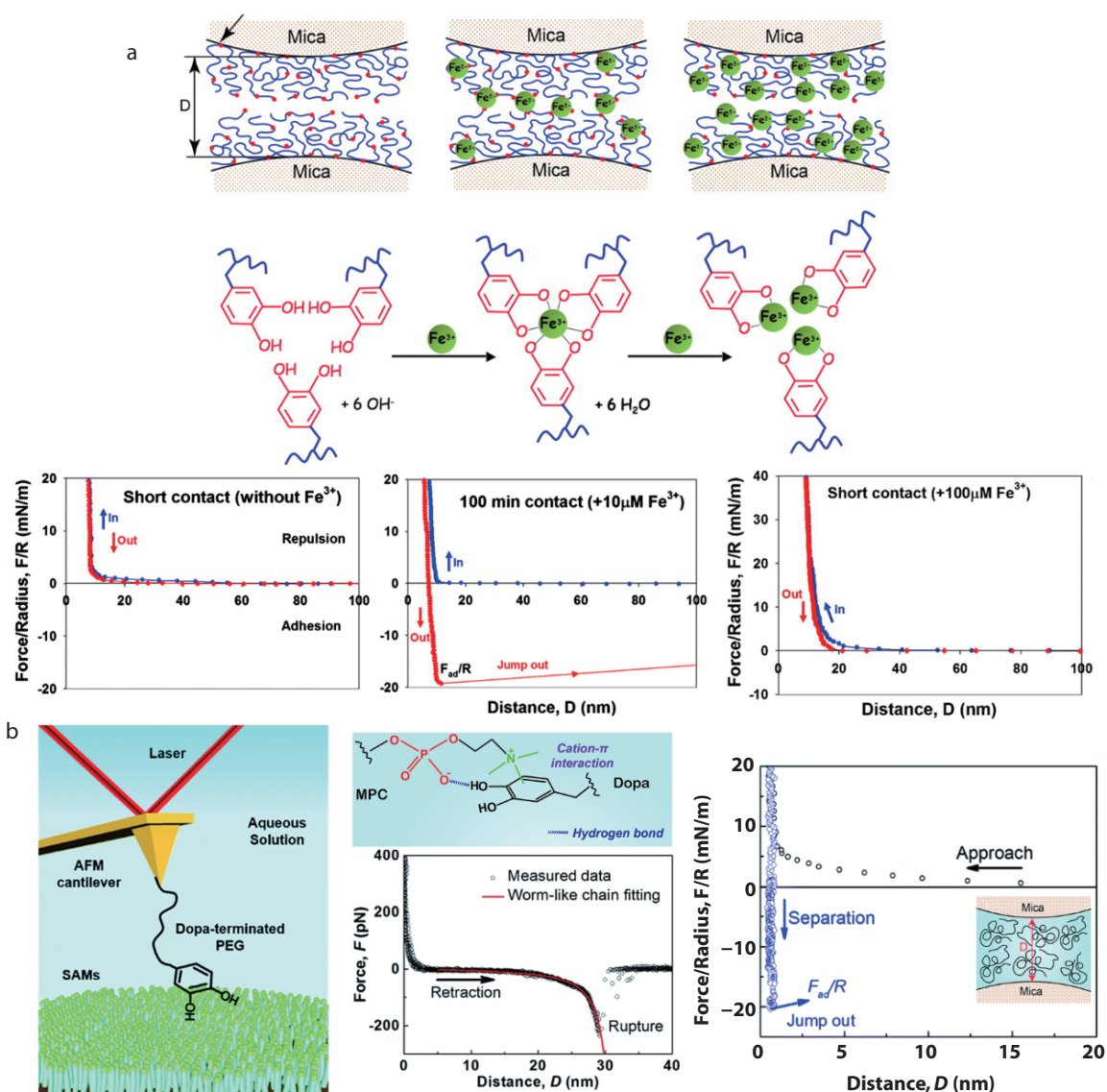


Fig. 4 (a) Measuring of the interaction forces between byssal cuticle protein (mfp-1) in Fe³⁺ aqueous medium using SFA. (Reproduced with permission from Ref. [46]; Copyright (2010) National Academy of Sciences). (b) AFM-SMFS and SFA measurements of interaction between Dopa and zwitterionic MPC. (Reproduced with permission from Ref. [53]. Copyright (2019) The Royal Society of Chemistry).

action by measuring the interaction forces between byssal cuticle protein (mfp-1) in aqueous solution with Fe^{3+} ions using SFA (Fig. 4a), and demonstrated that this interaction provides a novel approach for developing self-healing materials underwater and is important for curing of mussel foot proteins.^[46] Mfp-1 is a DOPA-rich (containing 13 mol% of Dopa) and highly positively charged ($pI \sim 10$) protein, which does not show noticeable cohesion. In the force measurements, mfp-1 was coated on two mica surfaces and the surface interactions were measured in the absence and presence of iron (III) ions of different concentrations. As shown in the force-distance profiles in Fig. 4, no apparent attraction or adhesion was measured between two mfp-1 coated mica surfaces. In contrast, with the addition of 10 $\mu\text{mol/L}$ Fe^{3+} , significant and reversible adhesion was detected when two mfp-1 layers were brought into contact and separated. Moreover, the adhesion force increased with increasing the contact time. For 100 min contact time, the equivalent adhesion energy per unit area between two flat surfaces, W_{ad} (calculated using $F_{\text{ad}} = 1.5\pi RW_{\text{ad}}$), reached 4.3 mJ/m^2 , indicating high bridging strength between mfp-1 molecules due to their coordination interaction with Fe^{3+} ions. Raising Fe^{3+} concentration to 100 $\mu\text{mol/L}$ led to the abolition of the adhesion force, because the triscatecholato-iron complexes at lower Fe^{3+} concentrations changed to nonbridging monocatecholato-iron interaction. Cation- π interaction between benzene rings of Dopa and positively charged residues of proteins, and π - π interaction between Dopa phenyl groups have also been found to contribute to the cohesion of some mussel foot proteins (*i.e.*, mcfp-1) by force measurement through SFA.^[67,84] The strong cation- π interactions inspired by marine mussel adhesives are able to drive the complexation and coacervation (liquid-liquid phase separation) of even like-charged polyelectrolytes, *i.e.*, the recombinant mussel foot protein (rmfp-1) and poly(2-(trimethylamino)ethyl methacrylate),^[85] or a single cationic protein rmfp-1 in natural seawater conditions.^[86] Also, owing to the cation- π interaction, self-polymerized catecholamine coatings have been found to demonstrate a adhesive strength 30 times higher than that of poly(catechol) coatings by force measurement through SFA. Gong *et al.* have developed an adhesive hydrogel working in saline water based on the cationic-aromatic interaction.^[87] Israelachvili and coworkers identified the self-healing mechanism of their metal-free catechol-functionalized polyacrylates to be the hydrogen bonding between interfacial catechol moieties using SFA.^[88] The adhesion force between two catecholic soft polymer surfaces was measured to be 700 mN/m (contact time of 5 s) by SFA, which was larger than that between polymers with catechol moieties blocked by silyl groups or oxidized to quinone. Very recently, by using SFA to systematically measure the adhesion of poly(catechol) (PC) surfaces under various saline conditions, we have identified that ternary π -cation- π interaction played an important role in enhancing the binding force of π -conjugated catecholic adhesive in the presence of salt cations.^[72] Another type of interaction, the anion- π interaction, has been first quantitatively measured by our lab between anionic phosphate ester and π -conjugated poly(catechol) moieties using SFA and recognized to indispensably contribute to the wet adhesion of Dopa-mediated

bioadhesives.^[71]

Recently, by employing another nanomechanical technique, AFM-based single-molecule force spectroscopy (AFM-SMFS), we measured the interactions between Dopa and zwitterionic 2-methacryloyloxyethyl phosphorylcholine (MPC) that is well known for its outstanding anti-fouling property.^[53] The force measuring principle of AFM is very similar to that of SFA. As illustrated in Fig. 4(b), the AFM tip and substrate were modified with target molecules, *i.e.*, Dopa-terminated PEG and MPC, respectively. The force-distance curves were obtained by driving the functionalized AFM tip to approach and then retract from the modified substrate. The deflection of the AFM cantilever was detected through a reflected laser beam onto a 4-quadrant photodiode detector, and the force was determined from the deflection and the spring constant of the cantilever *via* the Hooke's law. Representative force-distance curve between Dopa and zwitterionic MPC is shown in Fig. 4(b), and a single-molecule rupture event is visible at a distance around 29 nm (close to the contour length of Dopa-PEG) upon retraction of the tip, resulting in a statistically averaged rupture force of 216.2 ± 9.2 pN. The dissociation energy for the single Dopa moiety interacting with MPC was calculated to be $\sim 19.4k_{\text{B}}T$, which is larger than those of other zwitterionic (*e.g.*, $-(\text{CH}_3)_2\text{N}^+(\text{CH}_2)_3\text{SO}_3^-$), cationic (*e.g.*, $-\text{N}^+(\text{CH}_3)_3$) or anionic (*e.g.*, $-\text{SO}_3^-$) molecules due to the formation of synergistic cation- π and hydrogen bonding interactions. A random copolymer of MPC and Dopa was further synthesized and demonstrated strong cohesion of 7.2–14.1 mJ/m^2 as measured by SFA, which might shed light on the future design of novel zwitterion/Dopa-mediated self-healing hydrogels. In another work, we have developed a universal mussel-inspired anchoring strategy based on a cationic amine-modified catechol ligand with the amino group at an adjacent position.^[89] AFM-SMFS reveals its enhanced anchoring stability compared to traditional catechol anchors. The amine-modified catechol ligand was further coupled with the MPC moiety for substrate-independent fabrication of anti-fouling coatings with excellent ultrasonic stability. This strategy might be applied to functionalize catechol-containing hydrogel materials.

UPY-BASED HYDROGELS

Inspired by the assembly behaviors of biological molecules (*e.g.*, double-helical DNA and protein β -sheets), complementary multiple hydrogen bonds have been increasingly used in the self-assembly of supramolecular structures and materials.^[90–92] Considering the insufficient stability of many multiple hydrogen bonds, Meijer and co-workers found that UPy could dimerize strongly (dimerization constant $K_{\text{dim}} > 10^6 \text{ M}^{-1}$ in CHCl_3) in a self-complementary DDAA (donor-donor-acceptor-acceptor) array of four cooperative hydrogen bonds (Fig. 1a).^[93] Prompted by this finding, they further use units of UPy as the associating end group in reversible self-assembling polymers.^[94] The quadruple hydrogen bonding formed by UPy is reversible, strong, directional and thermo-responsive, which makes it widely used for the fabrication of self-healing functional materials including bulk polymers^[95–98] and hydrogels^[99–102] in recent years. For example, we recently developed a conductive and self-healing elastomer based on quadruple hydrogen-bonding between

copolymers of poly(ethylene glycol) methyl ether methacrylate (PEGMA) and UPy-functionalized monomer.^[96] The resulted elastomer exhibited rapid self-healing of the mechanical and electrical properties within 5 min after inflicted damage, and has been successfully used as an adhesive strain sensor for the detection of large human movements and subtle physiological signals.

The hydrogels solely cross-linked *via* UPy groups are mechanically weak because the stability and lifetime of the dimers formed by the UPy motif would be greatly reduced in polar solvent like water.^[103–105] Therefore, to enhance the mechanical performance of UPy-based hydrogels, other reversible bonds such as hydrophobic associations and electrostatic interactions were introduced to achieve improved mechanical properties. For instance, Vlassak *et al.* have developed an UPy-crosslinked hydrogel that could be stretched more than 100 times its original length as well as showed fast self-healing capability by combination of UPy binding with hydrophobic interaction.^[101] In this hydrogel, the UPy moieties were protected by hydrophobic pockets formed from sodium dodecyl sulfate (SDS) micelles, which avoided their dimer dissociation by water. We recently prepared a self-healing, injectable and conductive hydrogel incorporating multiple hydrogen-bonding UPy and Fe³⁺ coordination as cross-linking points.^[102] As schematically illustrated in Fig. 5(a), the UPy-functionalized monomer (UPyMA) was copolymerized with a hydrophilic anionic monomer, 4-styrenesulfonic acid sodium salt, to form the first network of the hydrogel *via* quadruple hydrogen-bonding between UPy, followed by the addition of aniline, a conjugated polymer precursor. Further addition of Fe³⁺ not only triggered the *in situ* polymerization of aniline to generate conductive networks, but the Fe³⁺ also chelated with anionic sulfonic groups on the copolymers *via* electrostatic interaction to reinforce the hydrogel network. The resulted hydrogel is stretchable and elastic at room temperature whilst turns into a liquid-like material above 45 °C due to the thermo-induced stability reduction of the UPy dimers. As shown in Fig. 5(b), the shear moduli and viscosity of the hydrogel were greatly reduced upon heating with the loss modulus surpassing the storage modulus above 45 °C, indicating the liquid-like material state at elevated temperatures. This enables the hydrogel to be mouldable and injectable at high temperatures. Owing to the reversible physical cross-linking strategies, the hydrogel demonstrated excellent self-healing property, *i.e.*, two hydrogel segments merged into one piece within a few seconds with a well-bonded interface that could withstand stretching (Fig. 5c). The superior conductivity (13 S/m) and linear and sensitive response to applied tensile strains enable the hydrogel to be used as a wearable electronic sensor to detect diverse human motion signals (Fig. 5d).

By employing AFM-based SMFS, we have investigated the binding behaviors of the UPy dimeric complexes in aqueous environment.^[103] Since the stability of UPy dimers would be seriously diminished in polar solvents while hydrophobic pockets could protect the UPy moieties, the effect of hydrophobic interactions on the intermolecular hydrogen bonding has also been studied. The AFM-SMFS experimental setup for quantifying the UPy interactions was shown in Fig. 5(e). Both the AFM tip and Au substrate were coated with UPy-function-

alized PEG, where hydrophobic alkylene spacers of different lengths were tethered between PEG and UPy moieties. According to the force-extension curves (Fig. 5e), the rupture forces and binding energies of UPy dimers increased with the spacer length. The dissociation force and binding free energy reached 104 pN and 32.4 kJ/mol, respectively, for UPy dimerization with the longest adjacent hydrophobic fragment of 12 carbon atoms. The force measurement of the UPy interactions in aqueous solution deepens the fundamental understanding of this bond and provides practical insights into the future design of UPy-based self-healing hydrogels.

SCHIFF BASE BONDS CROSS-LINKED HYDROGELS

Imine bond ($-N=CH-$, Fig. 1f) is a dynamic chemical bond formed from the condensation reaction between aldehydes and primary amines. The imine formation reaction was discovered by Schiff^[106] in 1864, and thereby imines are also referred to as Schiff bases. Hydrolysis of the Schiff base would take place under acidic conditions.^[107–109] The bond is reversible and dynamic under mildly acidic to slightly basic conditions due to the imine hydrolysis/reformation reaction reaching a dynamic equilibrium and the rapid imine exchange reaction occurring under such conditions.^[37,108,110] Owing to their ready formation and dynamic nature under neutral conditions, and stimulus-responsive properties, Schiff base bonds have been extensively adopted in the fabrication of functional self-healing hydrogels. Hydrogels based on natural macromolecules bearing primary amino groups like chitosan^[111–116] and gelatin^[117,118] crosslinked by aldehydes like oxidized polysaccharide^[114,117] and synthetic benzaldehyde-modified difunctional PEG (DF-PEG)^[111–113] have been widely reported, and applied in various biomedical applications like wound healing,^[115,116] drug or cell delivery,^[113,118] and central nervous regeneration.^[112]

We have developed a series of imine-crosslinked hydrogels based on synthetic polymers with expanded applications including biomedical, environmental and electronic engineering. SFA was employed to measure the force magnitudes and reversibility of the Schiff base bonds, the self-healing process and the stimulus-responsive mechanisms of the developed hydrogels. Through the Schiff base reaction between branched polyethylenimine (PEI) and DF-PEG, we have prepared a hydrogel that can self-heal to rapidly recover its integrity and mechanical properties after damage, as shown in Figs. 6(a) and 6(b).^[119] The force magnitude of the Schiff base interaction between two hydrogel components was investigated by SFA with positively charged PEI coated on two mica surfaces followed by injection of DF-PEG between the surfaces. A strong adhesion force was measured to be ~12 mN/m, about 17 times stronger than that between unmodified PEG and PEI, indicating the formation of imine bonding. The Schiff base chemistry is reversible as evidenced by the adhesion force of the same magnitude in sequential approach-separation force measurements. Interestingly, the hydrogel also exhibits a reversible strain-stiffening behavior, *i.e.*, becoming stiffer with the increase of applied stress or strain, which may effectively prevent damage when subjected to large deformations but has rarely been reported in synthetic

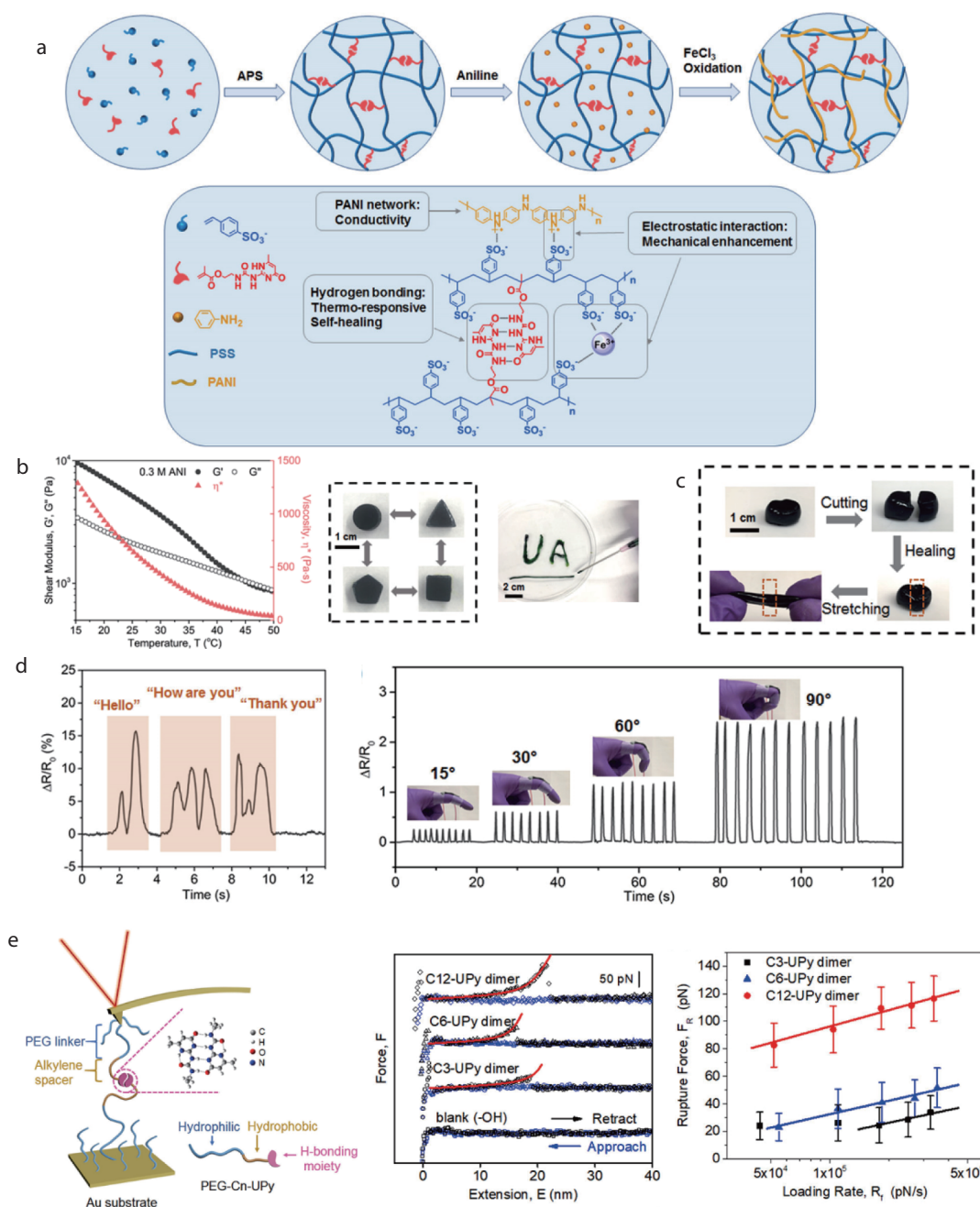


Fig. 5 (a) The hydrogel incorporating multiple hydrogen-bonded UPy and electrostatic interactions (between polyaniline and sulfonic groups, and Fe^{3+} and sulfonic groups) as cross-linking strategies and the demonstration of its (b) thermo-induced mouldability and injectability, (c) self-healing capability and (d) sensing performances. (Reproduced with permission from Ref. [102]; Copyright (2019) American Chemical Society). (e) AFM-SMFS force measurements of the UPy dimeric complexes in aqueous environment. (Reproduced with permission from Ref. [103]; Copyright (2019) American Chemical Society).

flexible polymer hydrogels (Fig. 6c). This strain-stiffening property of the PEI/PEG hydrogel can be readily tuned by changing the gelator concentration, temperature and cross-linker (DF-PEG) chain length. This hydrogel system was further used for the treatment of mature fine tailings (MFT), a wastewater slurry from the warm water-based bitumen extraction from Canadian oil sands (Fig. 6d).^[120] The dewatering of wastewater with high concentrations of colloidal solids,

like MFT, remains a challenge due to the extremely stable nature of concentrated colloidal suspensions. For the treatment of MFT, first, PEI and DF-PEG were directly mixed with MFT to form a double crosslinked hydrogel *via* electrostatic interactions between PEI and negatively charged suspended solids in MFT and imine bonds. These two interactions were validated by SFA with the adhesion energies for the electrostatic interaction and Schiff base reaction measured to be 3.8

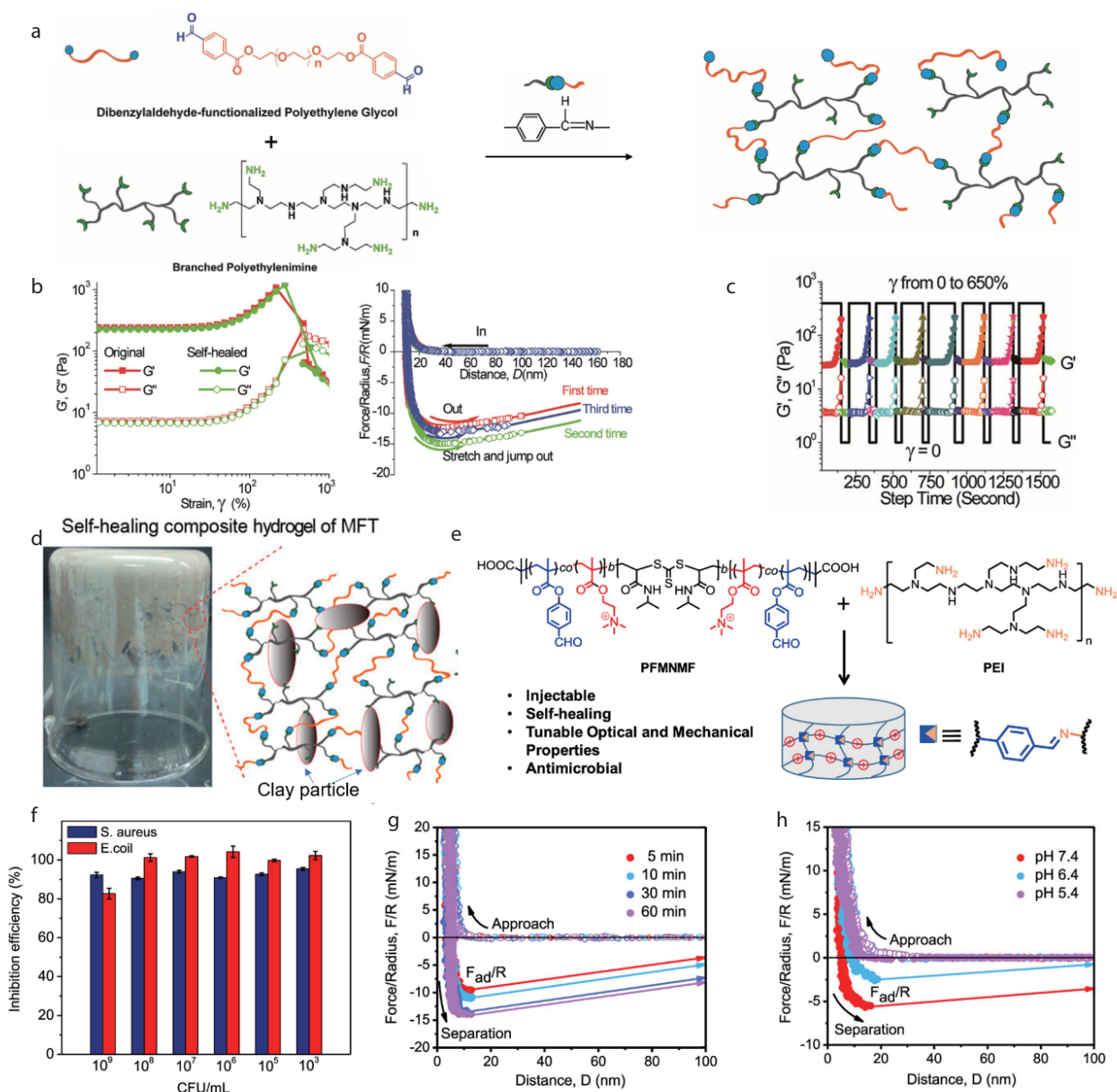


Fig. 6 (a) The PEG/PEI hydrogel crosslinked by dynamic imine bonds and the demonstration of its (b) self-healing and (c) strain-stiffening properties. (Reproduced with permission from Ref. [119]; Copyright (2017) American Chemical Society). (d) The imine-based PEG/PEI hydrogel used for MFT treatment. (Reproduced with permission from Ref. [120]; Copyright (2019) American Chemical Society). (e) The hydrogel formed by Schiff base reaction between PEI and a benzaldehyde-functionalized ABA block copolymer, (f) demonstration of its antimicrobial performance, and SFA measurements of (g) the self-healing and (h) pH-responsive properties of the hydrogel. (Reproduced with permission from Ref. [121]; Copyright (2019) American Chemical Society).

and 12.3 mN/m, respectively. By vacuum filtration and mechanical compression of the composite hydrogel, a water release of 80% was achieved with a low solid content at the ppm level in the released water, owing to the effective trapping of fine particles and small flocs by the polymer network. This work opens up the opportunity for rapid release of high-quality water from wastewater slurries.

Another multifunctional imine-based self-healing hydrogel was fabricated by mixing branched PEI with a benzaldehyde-

functionalized ABA block copolymer, as shown in Fig. 6(e).^[121] The copolymer is composed of a central B block of thermosensitive PNIPAM and two terminal A blocks randomly polymerized from a trimethylammonium-containing cationic monomer and an aldehyde-bearing monomer. The developed hydrogel was not only self-healing but also possessed multiple desirable features for biomedical applications like injectability, antimicrobial capability (Fig. 6f), biocompatibility, and dual pH- and temperature-responsive-

ness. The interaction force between the two hydrogel components was measured by SFA, giving an adhesion energy between two polymers of 6.0 mN/m. Increasing contact time of two surfaces led to rises of the adhesion energy, reaching 14.0 mN/m at the 30 min contact time (Fig. 6g). Interestingly, the adhesion energy reached a plateau after the contact time increased to 30 min, which was attributed to the equilibrium of the imine reaction cross the two surfaces. The time well agreed with the self-healing time of bulk hydrogels, shedding light on the self-healing mechanism at nanoscale. In addition, lowering pH from 7.4 to 5.5 resulted in the diminishment of the adhesion between two surfaces in SFA, elucidating the pH sensitivity of the dynamic imine bonds at nanoscale (Fig. 6h).

Nanocomposite hydrogels based on Schiff base chemistry have also been developed by our lab for different applications. Self-healing and injectable hydrogels with pH responsiveness are great intelligent delivery systems for therapeutic agents such as drugs and proteins. We have prepared an injectable nanocomposite hydrogel with fast self-healing and ultra-sensitive mildly acidic pH-responsiveness through Schiff base linkages between aldehyde-functionalized PMPC and amine-modified silica nanoparticles (ASNP), as shown in Fig. 7(a).^[122] The gelation process of the hydrogel is extremely fast within 10 s, which indicates the instant bridging of nanoparticles by imine formation between the multiple readily accessible amino groups on ASNP surfaces and aldehydes on copolymers. This hydrogel shows degradation be-

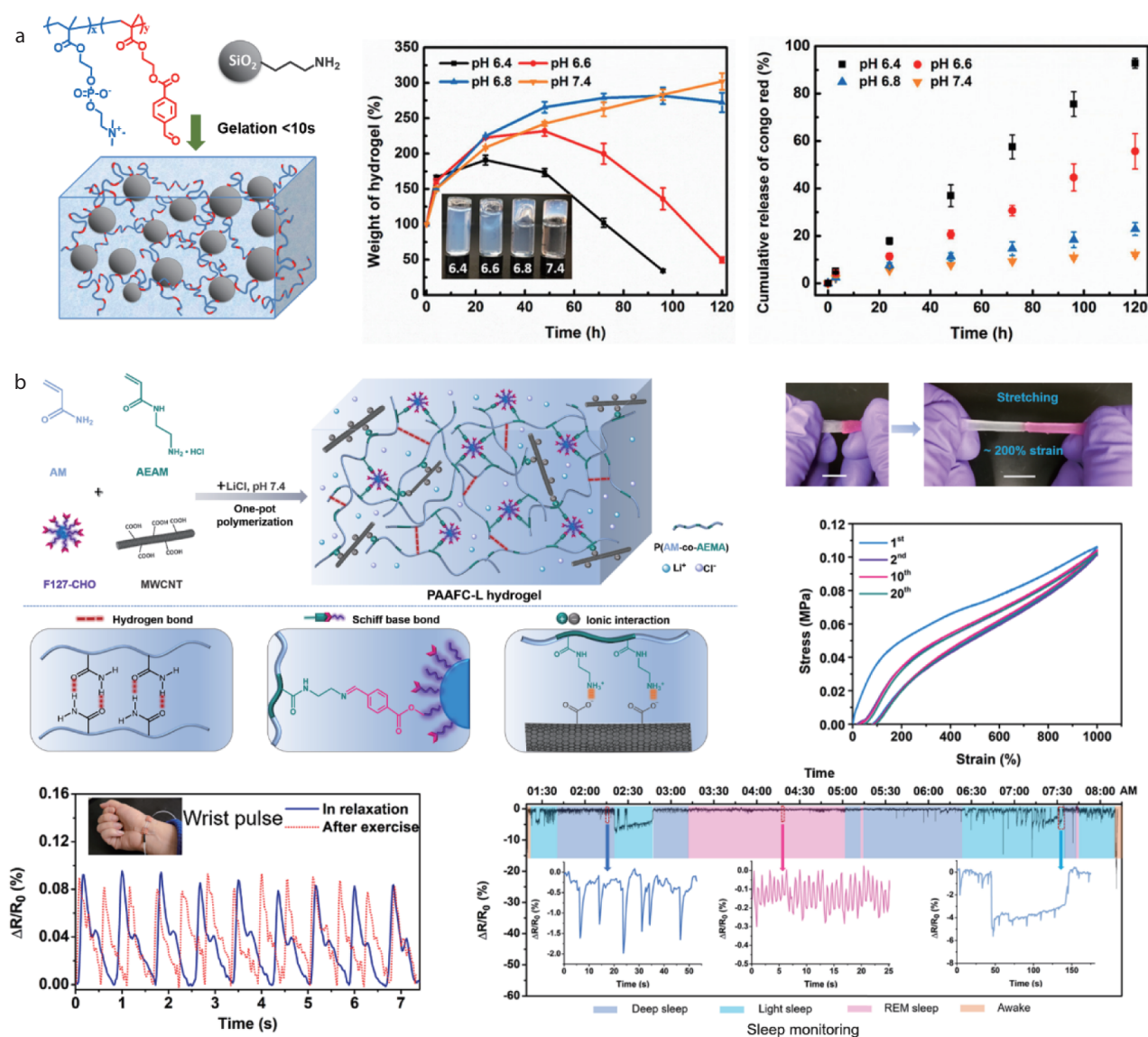


Fig. 7 (a) The hybrid self-healing hydrogel through Schiff base linkages between aldehyde-functionalized PMPC and amine-modified silica nanoparticles, and the demonstration of the ultrasensitive pH-responsiveness. (Reproduced with permission from Ref. [122]; Copyright (2020) American Chemical Society). (b) The ionic conductive hydrogel based on the combination of hydrogen bonding, imine reaction and electrostatic interaction, showing excellent self-healing property, elasticity, and sensing performances for wrist pulse and sleep monitoring. (Reproduced with permission from Ref. [123]; Copyright (2020) The Royal Society of Chemistry).

havior at mildly acidic pH (below 6.8) whilst remains quite stable at neutral physiological pH of 7.4. Especially, a slight drop of the pH from 6.8 to 6.4 can cause significant changes of the hydrogel's rheological, dissolution and drug release behaviors. This ultra-sensitive pH-responsive behavior was attributed to the superhydrophilicity of MPC and moderate pK_a value of amino groups on ASNP ($pK_a=7.6$). This hybrid hydrogel with pH-sensitive behaviors in the mildly acidic range is ideal to be used for the release of drugs to local acidosis regions, such as sites of tumor, wound healing and ischemia. In another study, a self-healing and ionic conductive hydrogel was fabricated *via* one-pot polymerization of acrylamide (AM) and an amino-functionalized monomer (AEAM) in the presence of carboxyl-modified multiwall carbon nanotubes (MW-CNTs), aldehyde-terminated poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) (F127-CHO) and LiCl, as demonstrated in Fig. 7(b).^[123] The hydrogel displays excellent mechanical properties, self-healing capability and thermotunable transparency as a result of the integration of multiple reversible interactions, *i.e.*, intermolecular hydrogen bonds, imine linkages, electrostatic interactions and micelle hydrophobic associations. Particularly, the hydrogel is capable of repeatedly recovering from a high tensile strain of 1000%, owing to the micellar cross-linking combined with reversible cross-linking strategies, which results in good fatigue resistance of the hydrogel when used as a strain/pressure sensor. Moreover, compared with other wearable strain sensors made by hydrogels, this hydrogel sensor demonstrated impressive sensitivity and reliability for the acquisition of detailed waveform changes of radial artery pulses before and after exercise. We further integrated this composite hydrogel with a sleep eye mask to monitor subtle eye movements during human sleeping. The result suggests the feasibility for this device to detect different sleep stages and high reliability for the recognition of rapid eye movement (REM) sleep.

BORONIC ESTER-BASED HYDROGELS

Boronic ester bond (Fig. 1g) is another dynamic covalent bond that has been widely used in the preparation of self-healing hydrogels. Boronate esters are generated by the condensation of boronic acid compounds and 1,2-/1,3-diols. The hydrogel networks formed by this type of bonds are considered to be transient due to the reversible hydrolysis and reformation of the boronic acid-diol complexes under certain conditions.^[124] The gelation and self-healing properties of boronic ester-based hydrogels are closely related to the pH of the system, because the boronic ester formation is favored at the pH near or higher than the pK_a of boronic acids, and the exchange between the boronic esters and the starting components is most effective with the pH near the boronic acid pK_a .^[125–128] Deuel *et al.* reported the first borate-diol crosslinked hydrogel upon mixing borax and poly(vinyl alcohol) (PVA) around seven decades ago.^[129] Until now, numerous boronic ester-based hydrogels have been developed through the reactions between borax^[130–132] or phenylboronic acids (PBAs)-functionalized polymers^[128,133–135] and different diols (*e.g.*, PVA,^[131,136] sugar moieties-modified polymers or glycopolymers,^[137,138] catechol-containing polymers^[127,128,139]). One challenge for the fabrication of hydrogels *via* boronic acid-diol complexation is

the gelation normally occurred under alkaline conditions, which may impede their further use in biomedical applications. Tremendous efforts have been dedicated to address this issue with several strategies developed: using diols with high affinity for boronic acid at lower pH like salicylhydroxamic acid moiety;^[133] making use of PBAs with intramolecular coordination to stabilize the boronate ester formation such as 2-acrylamidophenylboronic acid;^[127] using PBA derivatives with lower pK_a like benzoxaborole with pK_a value ~ 7.2 ;^[128] increasing the pH of the microenvironment around the boronic acid by copolymerizing PBA-modified monomers with *N,N*-dimethylaminopropyl acrylamide.^[140]

Recently, we have developed a hydrogel through the boronic ester reaction between diphenylboronic acid-terminated PEG (DPB-PEG) and a glycopolymer, poly(acrylamide-*co*-2-lactobionamidoethyl methacrylamide) [P(AM-*co*-LAMEA)], as shown in Fig. 8.^[141] The gelation occurred rapidly within ~ 30 s under physiological conditions. Besides, similar to the aforementioned imine-crosslinked PEI/DF-PEG hydrogel, this hydrogel demonstrated reversible and reproducible strain-stiffening behavior. The intensity of the strain-stiffening response increased as the boronic acid/sugar molar ratio or the polymer concentration decreased. The strain-stiffening behavior was ascribed to the nonlinear stretching and finite extensibility of the PEG, *i.e.*, PEG strands were stretched to be straightened before strain-stiffening while bending/stretching of the covalent bonds within the PEG strands occurred during the strain-stiffening stage (Fig. 8). The hydrogel also shows rapid self-healing capability. The healed gel could merge into one single piece within a few seconds and recover its original mechanical properties. When SFA was employed to quantitatively characterize the molecular interactions, a reversible adhesion of ~ 6.1 mN/m ($W_{ad} \sim 1.3$ mJ/m²) was measured between DPB-PEG and P(AM-*co*-LAMEA) while there was no adhesion between unmodified PEG and P(AM-*co*-LAMEA), indicating the reversible boronate complexations formed between two hydrogel components. This hydrogel was further used as a platform for 3D cell encapsulation and exhibited excellent biocompatibility.

SUMMARY AND PERSPECTIVES

In this work, we have reviewed our recent progress on self-healing hydrogels and quantified the related reversible molecular interactions using nanomechanical tools (*e.g.*, SFA and AFM). Self-mending hydrogels based on mussel-inspired bonding, UPy dimerization, Schiff base reaction and boronic ester bonds have been developed, which show some intriguing properties such as anti-fouling, injectability, antimicrobial, strain-stiffening, ultrasensitive pH-responsiveness, and excellent elasticity. These hydrogels have been used for diverse applications ranging from drug delivery and 3D cell culture to wearable strain sensors and wastewater slurries treatment. Moreover, we have applied nanomechanical techniques such as SFA and AFM to characterize the molecular interactions involved in mussel byssus and self-healing hydrogels. These force measurement studies have inspired the development of various self-healing hydrogels based on mussel chemistry and self-healing mechanisms established (*e.g.*, metal-biopolymer complexation such as Fe³⁺-catechol coordination, cation- π and

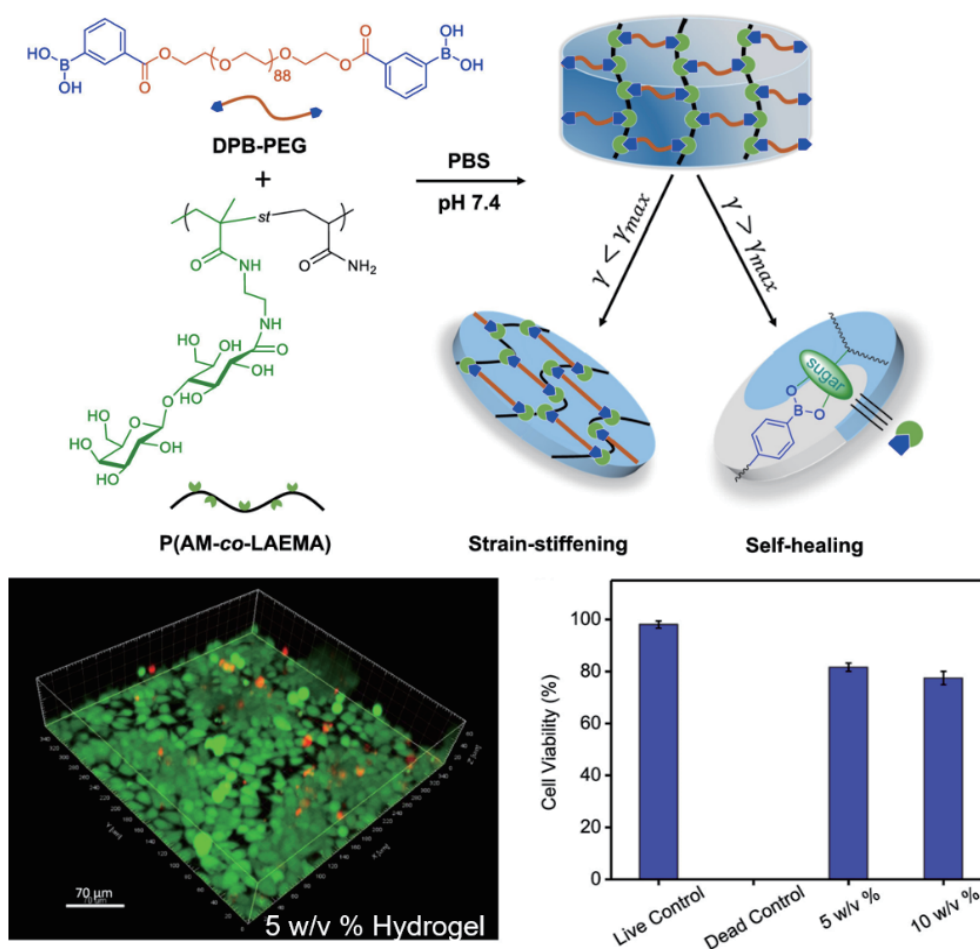


Fig. 8 The self-healing hydrogel via the boronic ester reaction between diphenylboronic acid-terminated PEG and the glycopolymer P(AM-co-LAEMA) and the demonstration of its application for 3D cell culture. (Reproduced with permission from Ref. [141]; Copyright (2020) American Chemical Society).

hydrogen bonding interactions). The quantification of the molecular interactions involved has helped to gain a fundamental understanding on the force magnitudes, self-healing mechanisms and stimuli-responsive behaviors of self-healing hydrogels, providing new insights into the design of novel self-healing materials. Although great progress has been achieved in the field of self-repairable hydrogels, several challenging issues remain to be tackled.

Despite the great number of self-healing hydrogels developed, it remains a challenge to prepare a hydrogel with the combination of excellent mechanical performances (*i.e.*, strong, tough and elastic) and complete and fast self-healing capability. Such materials might be achieved by combining multiple cross-linking mechanisms or developing new cross-linking strategies in the future. In addition, the applications of the majority of the hydrogels reported are in their preliminary stages. It is of great significance to move the applications of advanced hydrogels to a more practical stage, for example, from *in vitro* to *in vivo*, and from lab-scale demonstration to commercial products. On the other hand, most previous studies in the field focused on the development of new functional

self-healing hydrogels, and there are only limited fundamental studies and quantitative characterizations available on characterizing the underlying molecular interaction forces and self-healing mechanisms involved in hydrogel preparation. The quantitative characterization of such interaction forces and mechanisms at the molecular level or nanoscale will provide a foundation for the development of functional self-healing hydrogels and materials with tunable intermolecular and surface interaction behaviors.

BIOGRAPHY

Hong-Bo Zeng is a Professor in the Department of Chemical and Materials Engineering at the University of Alberta, a Tier 1 Canada Research Chair in intermolecular forces and interfacial science, a Fellow of the Canadian Academy of Engineering and a Member of the Royal Society of Canada's College of New Scholars. He received his BSc and MSc under the supervision of Professor Xiaogong Wang at Tsinghua University, and obtained his PhD in chemical engineering at University of California, Santa Barbara under the supervision

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