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REVIEW

Functional Conductive Hydrogels for Bioelectronics

Fanfan Fu, Jilei Wang, Hongbo Zeng,* and Jing Yu*

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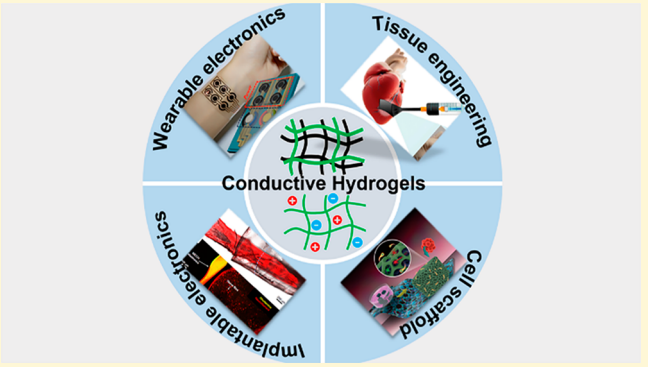
ABSTRACT: Conductive hydrogels are widely used in various applications, such as artificial skin, flexible and implantable bioelectronics, and tissue engineering. However, it is still a challenge to formulate hydrogels with high electrical conductivity without compromising their physicochemical properties (e.g., toughness, stretchability, and biocompatibility). Additionally, incorporating other functions, such as self-healing, shape memory, and wet adhesion, into conductive hydrogels is critical to many practical applications of hydrogel bioelectronics. In this Review, we highlight recent progress in the development of functional conductive hydrogels. We, then, discuss the potential applications and challenges faced by conductive hydrogels in the areas of wearable/implantable electronics and cell/tissue engineering. Conductive hydrogel can serve as an important building block for bioelectronic devices in personalized healthcare and other bioengineering areas.



Bioelectronics interfacing with human body/organ has emerged as a bridge to explore physiological information in our daily lives. Owing to their multifunctionality in personalized health monitoring, bioelectronics have been widely employed in various biomedical applications, including electronic skin,[1−5] wearable/implantable devices,[6−11] and soft robotics.[12−14] Currently, most bioelectronics devices are based on inorganic materials with appropriate electrical conductivity, such as metals and silicon.[15−20] However, the chemical and mechanical properties of those inorganic materials are strikingly different from these of biological tissues, which can lead to some serious problems during the implement of the inorganic materials based bioelectronic devices, including nonconforming contact between the devices and the surface of skin or tissue, unreliable signal collection, as well as causing inflammatory responses the body.[21−23] Many of these problems cannot be easily solved by only using inorganic materials.

Conductive hydrogels have the potential to be an alternative option to traditional inorganic materials in bioelectronics owing to their proper electronic, mechanical, and chemical properties.

Conductive hydrogels have shown great potential in bioelectronics.[2,24−30] Conductive hydrogels can be synthesized using either only conductive polymers, for example, poly(3,4-ethylenedioxythiophene) (PEDOT) or polyaniline (PANI),[31,32] as the main component of the hydrogel matrix or incorporating conductive additives, such as conductive polymers, carbon nanotubes (CNTs), and metal nanowires into an existing nonconductive hydrogel matrix.[33−37] Conductive hydrogels have the potential to be an alternative option to traditional inorganic materials in bioelectronics owing to their proper electronic, mechanical, and chemical properties. The high-water content of hydrogels allows the transport of biological and chemical molecules, thus providing an extracellular matrix-like (ECM-like) environment to facilitate the exchange of biological molecules and markers across interfaces. The tunable chemical structure of the polymer network endows conductive hydrogels with tunable mechanical properties to match those of tissues (elastic modulus from 0.1 to 100 KPa).[38] Owing to their excellent properties, conductive

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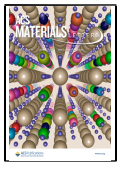

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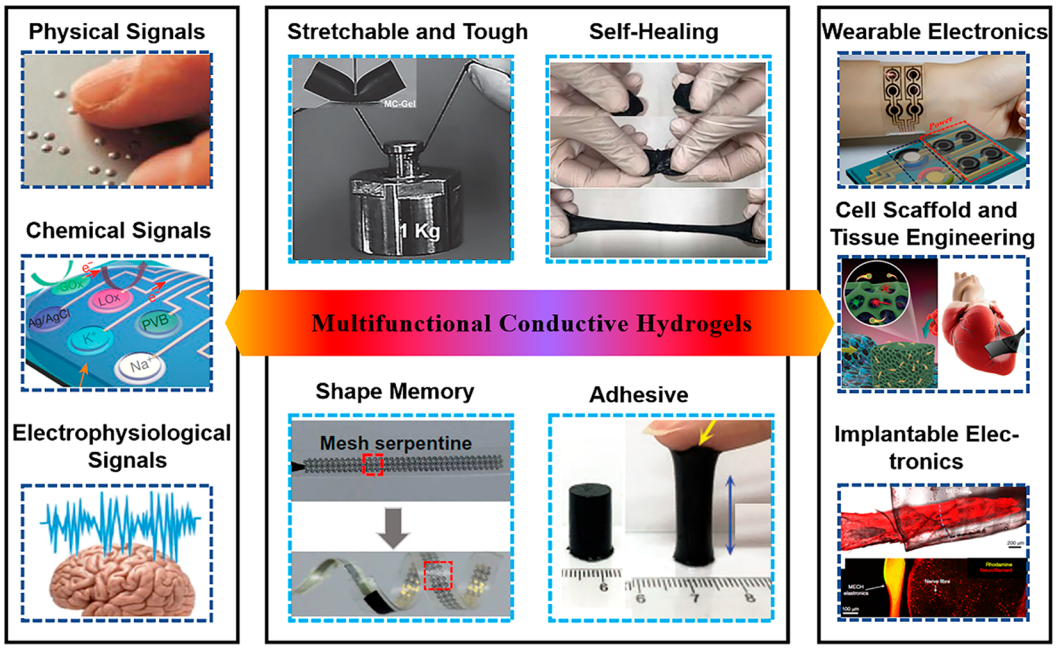

Figure 1. Functional conductive hydrogels for bioelectronics in biomedical applications. The left column presents the conductive hydrogels used for physical, chemical, and electrophysiological signals detection, respectively. [Reproduced with permission from refs 6 and 43. Copyright 2016 Nature Publishing Group and 2018 the Royal Society of Chemistry.] The middle column summarizes important functions of conductive hydrogels. [Reproduced with permission from refs 44−47. Copyright 2016 and 2018 Wiley-VCH and 2018 and 2019 AAAS.] The right column shows the application of conductive hydrogels in the areas of wearable electronics, cell scaffold and tissue engineering, and implantable electronics, respectively. [Reproduced with permission from refs 48−51. Copyright 2019 Elsevier, 2019 Nature Publishing Group, 2018 Wiley-VCH, and 2017 The Royal Society of Chemistry.]

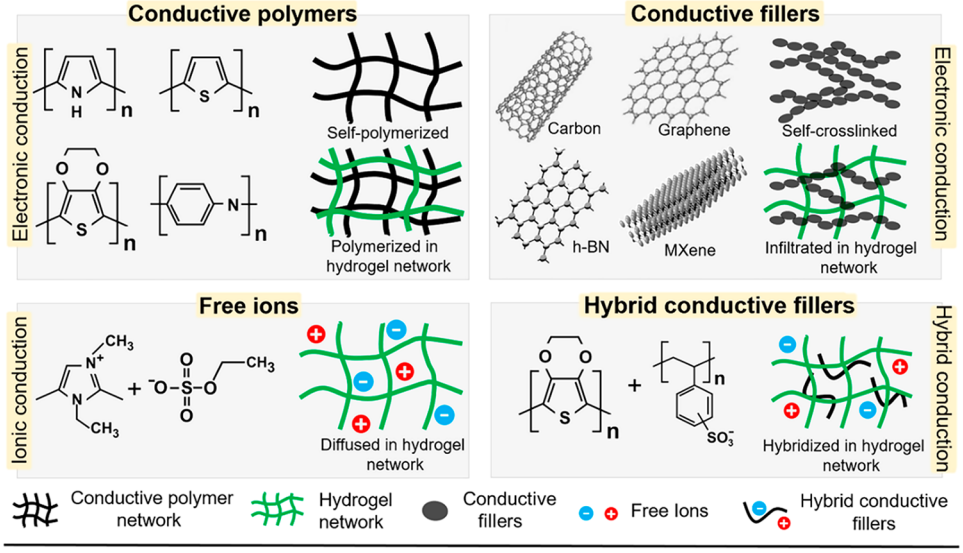

Figure 2. Structures of several types of conductive hydrogels. Conductive hydrogel can be synthesized by using conductive polymers, conductive fillers, free ions, and their mixtures. The formed hydrogels can be classified as electronic, ionic, and the hybrid electronic−ionic conducting hydrogels.

hydrogels have attracted great attention in biomedical applications such as wearable/implantable devices and bioelectronics at cell/tissue interfaces (Figure 1).

The main challenge for the development of conductive hydrogels for bioelectronics is to achieve high conductivity, while not to compromise the hydrogels' physicochemical properties, such as toughness, stretchability, and biocompatibility. For hydrogels based on pure conductive polymers, the conductivity originates from conjugated structures (conjugated π bond) of the conductive polymers.[39] Such conjugated structures are inherently rigid, which impairs the mechanical properties of conductive hydrogels. One strategy to prepare conductive hydrogels relies on mixing or in situ polymerizing conductive polymers within an existed nonconductive hydrogel matrix to form an interpenetrating conductive hydrogel network. However, such hydrogels suffer from low electrical conductivity because of the nonconductive hydrogel matrix in interpenetrating network acting as an electrical insulator.

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Another common strategy to improve the conductivity of the hydrogels is to add conductive fillers, such as CNTs, graphene, or metal nanoparticles/wires. This approach generally requires high contents of conductive fillers, which may cause phase separation of the hydrogel matrix and fillers, resulting in low stretchability, weak mechanical toughness, and poor fatigue resistance. Additionally, limited by their intrinsic weakness of inhomogeneous hydrogel networks, most of the previously reported conductive hydrogels are not able to sustain cyclic/multiple loading-unloading cycles. To achieve high conductivity and high toughness is, therefore, one major goal in the design of conductive hydrogels.

Developing multifunctional conductive hydrogels is also critical to the success of hydrogel bioelectronics. Various functionalities, such as self-healing, strong tissue adhesion, and shape memory, can be incorporated into conductive hydrogels via tuning the chemical composition and physical structure of the hydrogels.[40−42] This Review first reviews recent progress in multifunctional conductive hydrogels for bioelectronics and tissue engineering and, then, discusses the remaining challenges and obstacles in the field. This Review aims to provide useful insights and guidelines into the design and development of conductive hydrogels for various biomedical applications.

■ ENGINEERING FUNCTIONAL CONDUCTIVE HYDROGELS

Conductive hydrogels are usually prepared by (1) building single component hydrogel networks by self-polymerization or self-assembly of conductive polymers/fillers, (2) constructing interpenetrating hydrogel networks by doping conductive polymers/fillers, (3) diffusing free ions, and (4) embedding conductive fillers/free ions into an existing non-conductive hydrogel matrix (Figure 2). Depending on the conductive mechanism, the fabricated hydrogels can be classified as electronic,[39] ionic,[52] and hybrid electronic−ionic conductive hydrogels.[53] In general, conductive polymer-based hydrogels mainly rely on electronic conduction, as the conductivity origins from the conjugated π bond of the conductive polymers, such as PEDOT, PANI, polypyrrole (PPy), and polythiophene (PT).[39,54−56] Conductive filler-based hydrogels mainly rely on electronic conduction of the fillers, which are often graphene, CNTs, and metal nanoparticles/wires.[52,57−59] For those conductive hydrogels containing free ions such as salts and ionic liquids, they acquire ionic conductivity due to the migration of ions.[27,60] Notably, many conductive hydrogels possess both electronic and ionic conduction.[53] For example, poly(styrenesulfonate) (PSS) doped PEDOT (PEDOT:PSS) is commonly used to prepare conductive hydrogels with mixed electronic−ionic conduction because of the charge-conducting PEDOT backbone and ion-conducting PSS chains.[33] Conductive hydrogels could exhibit tailorable conductivity by designing an electronic, ionic, or hybrid conductive network in the hydrogel systems. To improve the conductivity, the most commonly used method is to construct a conductive network with long conjugated polymer chains for conductive polymer-based hydrogels, and to increase the density of the fillers for conductive filler-based hydrogels. In addition, advanced processing methods are widely used in the fabrication of functional conductive hydrogels, such as three-dimensional printing (bio-plotting printing, light-based printing, and inkjet printing),[30,61,62] electron-beam lithography,[63] and electrochemical gelation.[64]

Conductive hydrogels could exhibit tailorable conductivity by designing an electronic, ionic, or hybrid conductive network in the hydrogel systems.

Many bioelectronics devices require high stretchability and conductivity in order to function properly during the movement of human body, which presents a big challenge for the design of conductive hydrogels.[52,65−68] Increasing the content of conductive fillers could improve the conductivity of the hydrogel. However, this may lead to phase separation between hydrogel matrix and fillers, which results in low stretchability. For conductive polymer-based hydrogels, the conjugated structures of polymer are inherently rigid, which impairs the mechanical properties of the fabricated hydrogels. It is difficult for a hydrogel to own high stretchability and high conductivity simultaneously.

Various approaches have been employed to improve the stretchability of conductive polymer-based hydrogels.[33,64,69,70] PEDOT:PSS hydrogel exhibits moderate electrical conductivity and fracture strain (about 5%).[71] However, the strechability of a pure PEDOT:PSS hydrogel can be dramatically enhanced to over 35% by introducing an interconnected network of PEDOT:PSS nanofibrils using solvent annealing.[72] Alternatively, the stretchability of PEDOT:PSS hydrogels can also be enhanced by adding ionic liquid plasticizers (1-butyl-3-methylimidazolium octyl surfate) (Figure 3a), which results in a conductive hydrogel with a conductivity comparable to pure PEDOT:PSS (over 4100 S/cm) even under 100% strain.[73] Double/multi-network hydrogels have also been developed to achieve high strechability while maintaining the conductivity of the hydrogels. An interpenetrating polyaniline (PANI) and poly(acrylamide-*co*-hydroxyethyl methyl acrylate) (P-(AAm-*co*-HEMA)) double-network conductive hydrogel was fabricated with the assistance of hydrogen bond between hydrogel networks (Figure 3b).[74] The interpenetrating networks endowed high conductive hydrogel with outstanding strength (about 220% strain) and toughness (over 9 MJ/m^3), together with excellent linearity under high strain levels.

Engineering proper interactions between the hydrogel network and the conductive fillers can substantially enhance the toughness and stretchability of filler based conductive hydrogels.[75,76] Graphene oxide (GO) and CNT materials are widely used as fillers to prepare high stretchable conductive hydrogels benefited from their multi-functionality in building strong covalent/or non-covalent interactions with most polymer chains.[77,78] Lu et al. developed a stretchable polyacrymide-based (PAM) conductive hydrogel by introducing GO and polydopamine (PDA) into a PAM pre-gel solution. GO was converted into partially reduced graphene oxide (pGO) or fully reduced graphene oxide (rGO) through PDA reduction GO, forming a conducting pathway. The unreduced GO filler, PDA, and PAM are able to form strong non-covalent interactions, including hydrogen bonding, $\pi-\pi$ stacking, and electrostatic interactions (Figure 3c). Taking advantages of the non-covalent interactions, the prepared PDA-pGO-PAM hydrogel achieved impressive stretchability (extension ratio $\lambda = 35$), and good electrical conductivity (0.08 S cm^{-1}).[79] Additionally, macromolecular/micro-spheres, devised as zippable and energy-dissipating centers, have also been

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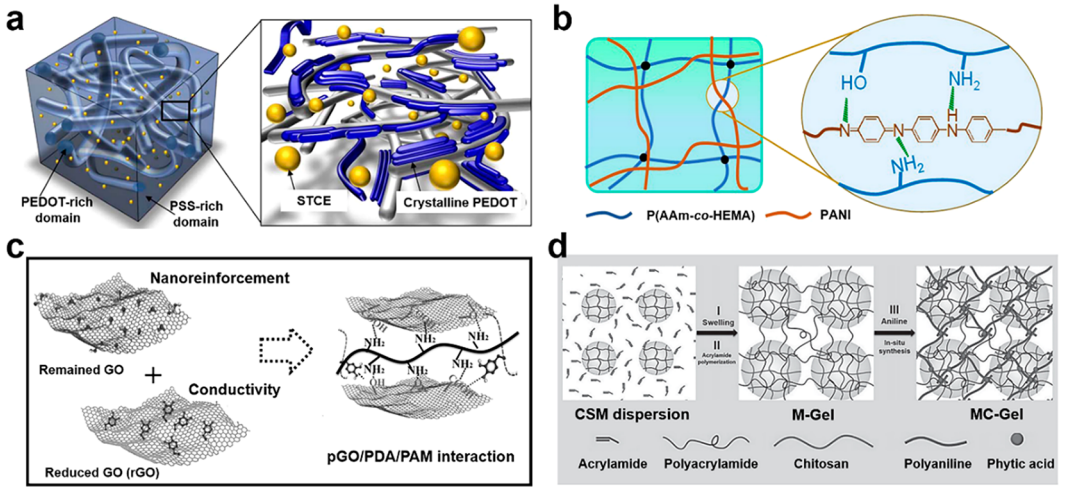

Figure 3. Schematic of tough and stretchable conductive hydrogels: (a) a highly stretchable conductive PEDOT:PSS hydrogel by incorporating ionic additives-assisted [Reproduced with permission from ref 73. Copyright 2017 AAAS], (b) an interpenetrating PANI/P(AAm-*co*-HEMA) hydrogels featured with high conductivity and stretchable ability [Reproduced with permission from ref 74. Copyright 2018 American Chemical Society], (c) a nanocomposite conductive hydrogel reinforced by pGO [Reproduced with permission from ref 79. Copyright 2017 Wiley-VCH], and (d) an ultra-stretchable conductive hydrogel formed by embedding chitosan microspheres into PAAm and PANI networks [Reproduced with permission from ref 44. Copyright 2016 Wiley-VCH].

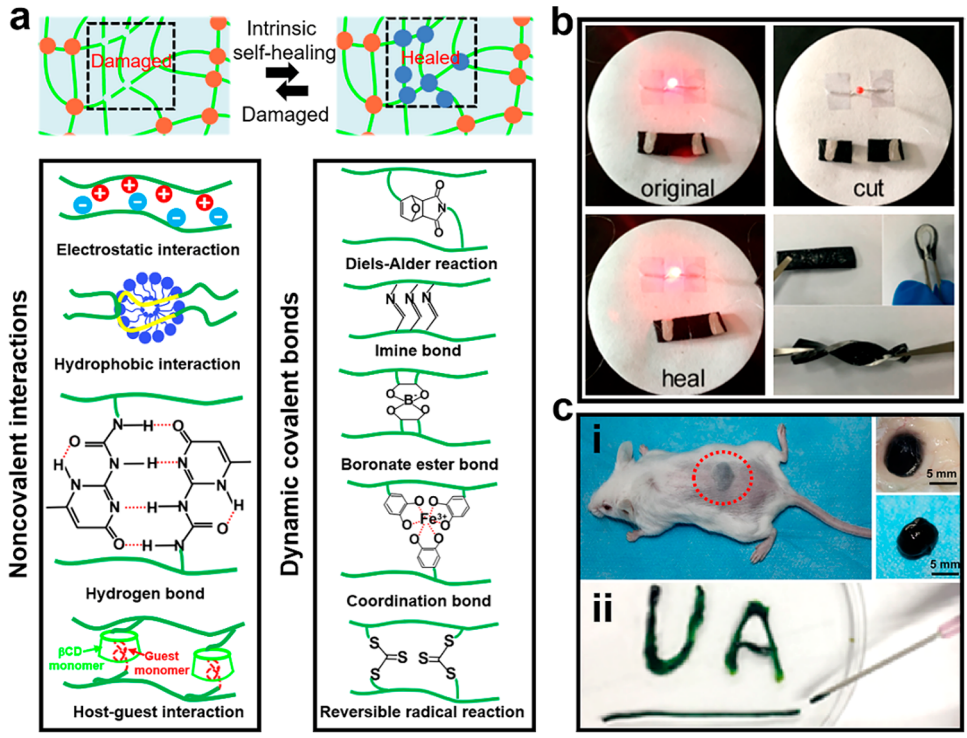

Figure 4. Self-healing and injectable conductive hydrogels. (a) Schematic illustration and mechanism diagram of fabricating intrinsic self-healing conductive hydrogels. (b) Self-healing conductive hydrogel based on transferring CNT film into a repairable carrageenan/PAAm hydrogel. [Reproduced with permission from ref 106. Copyright 2020 American Chemical Society.] (c) Injectable self-healing conductive hydrogels. The upper panel (i) shows the subcutaneous injection of a Dex-AT/CECS conductive hydrogel. [Reproduced with permission from ref 109. Copyright 2019 Elsevier.] The lower panel (ii) shows an injectable PANI/PSS-UPy conductive hydrogel that can pass through a needle and be molded into different shapes. [Reproduced with permission from ref 110. Copyright 2019 American Chemical Society.]

incorporated into conductive hydrogel networks to enhance the roughness of the hydrogels.[80] Zhang et al. synthesized a hydrogel with two-phase structure by in situ polymerization of polyacrylamide (PAAm) and PANI with chitosan microspheres (CSMs).[44] Because of the existence of energy-dissipating centers (CSMs) and interpenetrating double networks (PAAm and PANI) (Figure 3d), the formed conductive hydrogel exhibited extremely stretchability (626%), toughness (879 kPa), along with high conductivity (5 S m^{-1} with aniline concentration of 0.1 mol L^{-1}). Various other methods have also been utilized for preparing stretchable and tough conductive hydrogels such as those based on molecular sliding mechanism, pre-stretching/folding template,

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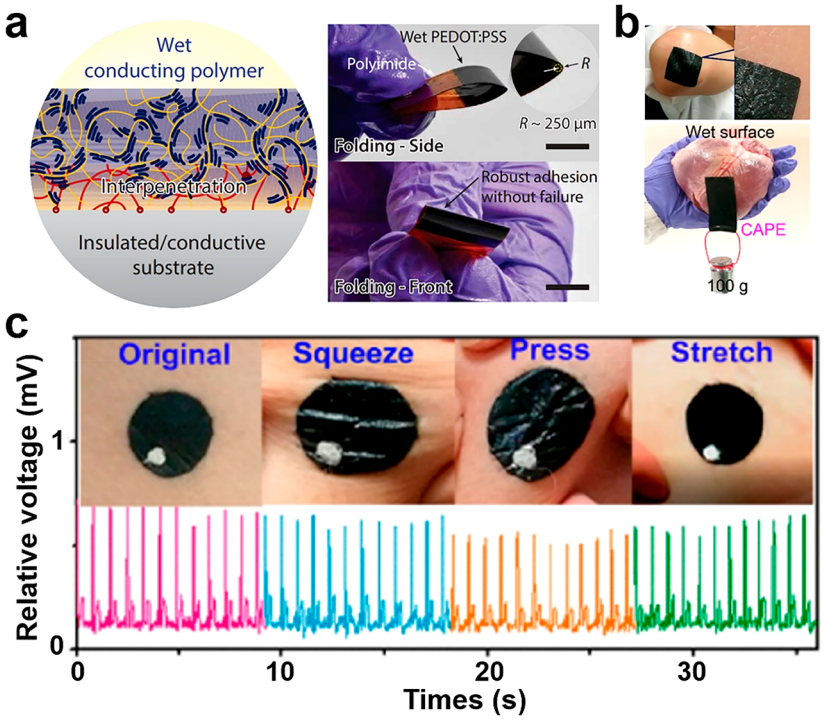

Figure 5. Adhesive conductive hydrogels. (a) Schematic and pictures showing adhesion of conductive polymer hydrogel on insulated/conductive substrates. [Reproduced with permission from ref 116. Copyright 2020 AAAS.] An adhesive conductive hydrogel fabricated by interfacial polymerized PPy and SF showing (b) adhesion on sweaty human skin and wet pig heart surface and (c) used for electrocardiography (ECG) signal monitoring upon different skin deformation. [Reproduced with permission from ref 117. Copyright 2020 American Chemical Society.]

and deformable structures (wavy, island-bridge, and serpentine).[81−87]

Conductive hydrogels with self-healing properties can significantly prolong the service time of bioelectronic devices and, thus, are very useful in a variety of applications, including cardiovascular repair, electronic skin, and soft robotics.[88−90] Many conductive hydrogels with high self-healing property are based on the intrinsic repair method via designing reversible (weak) interactions in the polymer networks. Under low external stress, the weak bonds can break first and adsorb the energy to protect the covalent polymer network. When the covalent polymer network of the hydrogel is damaged under higher external stress, the reversible bonds will reform to restore the properties of the hydrogel. Both noncovalent interactions including electrostatic interaction,[91] hydrophobic interaction,[92,93] hydrogen bond,[94] and host−guest interaction,[95] as well as dynamic covalent bonds such as Diels−Alder reaction,[96] imine bond,[97,98] boronate ester bond,[99] coordination bond,[100] and reversible radical reaction,[101] have been widely used to construct self-healing hydrogels (Figure 4a). The same strategies can be adopted in conductive hydrogel systems. For example, electrostatic interactions (between carboxylic groups, NH_2 groups, and ferric ions) have been incorporated in PPy-based conductive hydrogels to generate hydrogels with self-healing capabilities to restore the mechanical and conductive properties of the hydrogels.[102,103] Ren et al. reported a self-healing PPy/alginate-gelatin hydrogel based on the Schiff-base units formed between the aldehyde groups (form oxidized sodium alginate) and amines groups (from gelatin), which act as dynamic crosslinking points to repair the hydrogel.[104]

Other approaches have also been employed to develop self-healing conductive hydrogels. By introducing a conductive PPy network into an agarose hydrogel system, Jaehyun et al. developed an agarose/PPy-based self-healing conductive hydrogel responds to external stimuli.[105] Agarose undergoes a thermally reversible sol−gel transition (above 120 °C), which gives rise to a self-healing function to the hydrogel. The conductivity of the gel increases while the self-healing property deteriorates as a function of PPy concentration. Some self-healing conductive hydrogels are developed through the assistance of a substrate or composite material. For example, Han et al. reported a CNT-based self-healing conductive hydrogel with the assistance of a repairable carrageenan/PAAm hydrogel layer (Figure 4b).[106] A CNT film was transferred onto a carrageenan/PAAm hydrogel layer via a transfer printing process. The double helices of carrageenan can transfer to free coils at a temperature of above 50 °C, and reform new double helices below the melting temperature, which provides the self-healing capability to the carrageenan/PAAm hydrogel substrate. The mechanical properties of the hydrogel can be further improved by the large number of hydrogen bonds formed between the carrageenan and PAAm chains.

By properly controlling the gelation time, conductive hydrogels can be injectable.[107,108] Injectable conductive hydrogels can serve as tissue scaffold and delivery vehicles for electrical signal sensitive cell therapy, avoiding potential infection and pain caused by surgery. Hydrogels based on *N*-carboxyethyl chitosan (CECS) and dextran-grafted tetraanilin (Dex-AT) showed adequate electrical conductivity (10^{-2} mS cm^{-1}) and can be injected into rat subcutaneously for muscle regeneration and cell therapy (Figure 4c(i)).[109] Chen et al.

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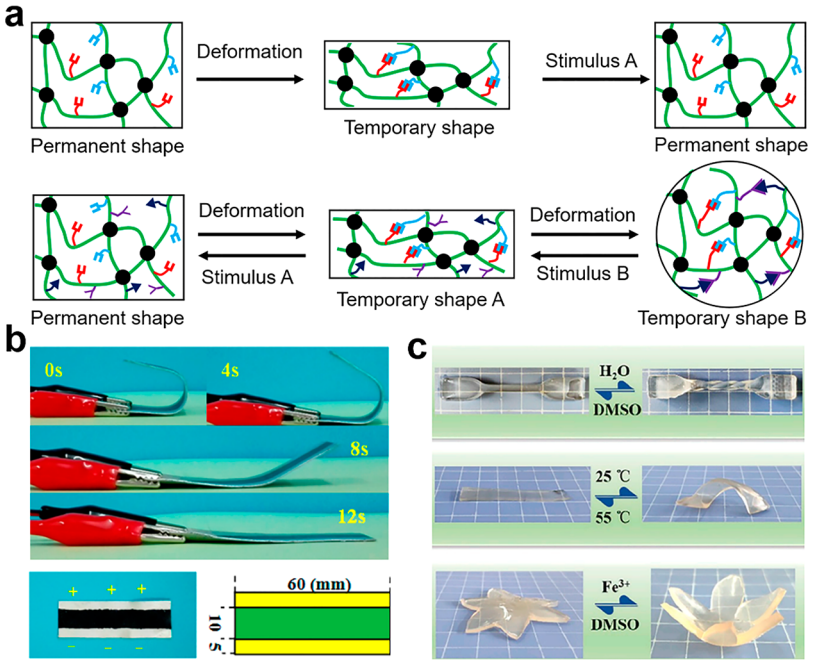

Figure 6. Shape memory conductive hydrogels. (a) Shape change mechanism of dual/multiple shape memory hydrogels. (b) Electro-stimulated shape memory conductive hydrogel based on CNTs and EVA/PCL. [Reproduced with permission from ref 122. Copyright 2016 American Chemical Society.] (c) Shape memory conductive hydrogel by constructing Fe^{3+} interactions in PVA/catechol hydrogel matrix. [Reproduced with permission from ref 123. Copyright 2020 Elsevier.] The formed shape memory conductive hydrogel exhibited shape memory behavior in response to multiple stimuli, including temperature, solvent and Fe^{3+} concentration.

developed an injectable self-healing conductive hydrogel by introducing 2-ureido-4[*1H*]-pyrimidinone (UPy) into a PANI/PSS polymer network (Figure 4c(ii)).[110] The UPy groups can form dynamic multiple hydrogen bonds with each other and serve as the crosslinking points of the PANI/PSS network. The formed conductive hydrogel can be molded into different shapes and injected through a needle.

Strong and sustainable adhesion to various surfaces, especially on wet biological tissue/organ surfaces, is critical to many in vivo applications of conductive hydrogel based bioelectronic devices.[111−114] Conductive hydrogels can achieve adhesion on various biological surfaces via different interfacial interactions, such as covalent bonds, hydrogen bonds, and physical entanglement.[45,115] However, to achieve strong adhesion on biological surfaces is challenging as the interfacial water may separate two surfaces at the molecular level and hinder the interactions. Designing proper interfacial interactions and controlling/utilizing the interfacial water are the two main approaches for engineering conductive hydrogel adhesives on both dry and wet surfaces.

By engineering proper interfacial interactions on both surfaces, conductive hydrogels can achieve strong adhesion to the target dry surface. For example, PEDOT:PSS hydrogels can adhere to diverse conducting and insulating substrates by adding a thin hydrophilic polyurethane (PU) adhesive layer between the dry substrate and wet hydrogel (Figure 5a).[116] To achieve strong adhesion, the substrate was functionalized with primary amine groups, which provide effective interfacial interactions (covalent bonds and/or electrostatic interactions) between the substrate and the adhesive PU polymer layer. Additionally, the interfacial water can swell the PU layer, which promotes the diffusion of PEDOT:PSS precursors into the PU matrix, forming an inter-penetrating polymer network between the two polymer layers.

Utilizing interfacial water from the wet and hydrogel surfaces to facilitate the formation of interfacial interactions is a main strategy for engineering conductive hydrogels with strong adhesion on wet surfaces. With proper water content (about 44%), the Young's modulus of natural silk fibroin hydrogel is similar to that of human skin, which enhances its adhesive ability to sweaty human skin and wet surface (pig heart) (Figure 5b).[117] When adhered to human skin, this SF/PPy conductive hydrogel can obtain a stable ECG signals under different skin deformation (squeezed, pressed, and stretched) (Figure 5c). Strong adhesion can also be achieved by controlling the gelation of the conductive hydrogels at the interface, as the precursors of the conductive hydrogel can diffuse through the interfacial water and penetrate into the target surface, subsequently forming an interpenetrating network upon gelation.[118]

Conductive hydrogels with shape memory function have great potential in applications, such as bioelectronics sensors, actuators, and soft robotics.[119−121] A shape memory hydrogel typically contains netpoints and stimuli responsive molecular switches. Upon external stimulation, the switches become flexible, and the netpoints are stable, resulting in an entropic elastic behavior of the hydrogel network that recovers from a temporary shape to its permanent shape (Figure 6a). Hydrogels responsive to multiple stimuli can be synthesized by including multiple types of switches, for example, temperature, light, and solvent responsive motifs, into the hydrogel polymer network.

The key obstacles for developing shape memory conductive hydrogels include to maintain a stable electrical performance during deformation and to ameliorate the weak mechanical properties and dull stimuli-responsive characteristics of the hydrogels. Thermoactivated shape memory conductive hydrogels could be achieved by incorporating conductive fillers (e.g.,

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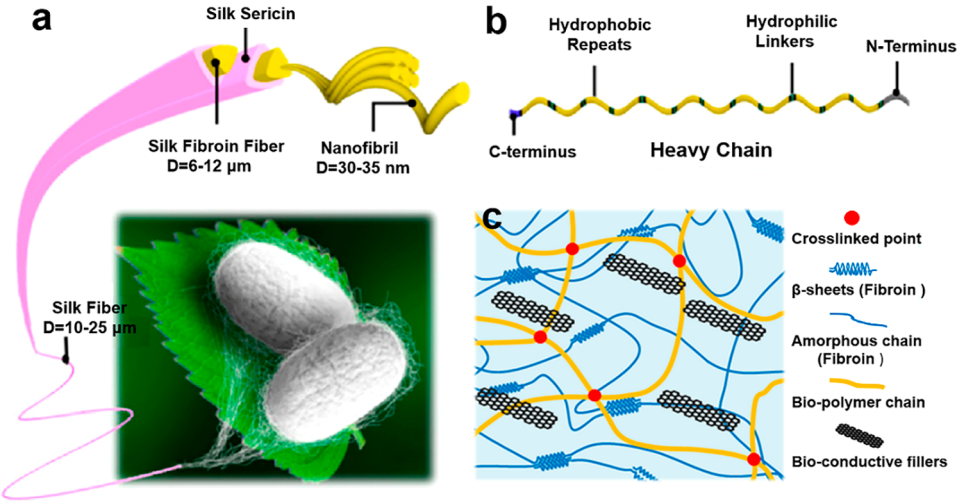

Figure 7. Biocompatible conductive hydrogels. (a) Hierarchical structure illustration of nature silk fiber. (b) Structure illustration of silk fibroin's heavy chain. [Reproduced with permission from ref 129. Copyright 2019 American Chemical Society.] (c) Schematic diagram of preparing an interpenetrating silk/biopolymer conductive hydrogel by doping with bio-conductive fillers.

CNTs, graphene platelets, and metal oxides) into a shape memory PU hydrogel matrix.[124] Similar approach was taken to fabricate an electroactivated hydrogel by blending CNTs into a poly(ethylene vinyl acetate)/poly(ε-caprolactone) (EVA/PCL) hydrogel matrix (Figure 6b).[122] Notably, introducing proper physical or chemical interactions can enhance the mechanical properties of shape memory conductive hydrogels. A 5,5,6,6-tetrahydroxy-3,3,3,3-tetramethyl-1,1-spirobisindane (TTSBI)-Fe^{3+}/poly(vinyl alcohol) (PVA) hydrogel matrix conductive hydrogel manifested strong mechanical properties because of the construction of hydrogen bonds, hydrophobic interactions, and metal coordination bonds in the hydrogel matrix (Figure 6c).[123] The hydrogel showed shape memory response to multiple stimuli, including temperature, solvent, and Fe^{3+} because of the crystalline domains of the PVA chains, solvent−polymer interactions, and catechol/Fe^{3+} interactions, respectively. To match the mechanical properties and geometrical features between the flexible electrode and nerve interface, a shape memory flexible electrode based on mesh serpentine Au and the mixture of polycaprolactone diol (PCL), poly(hexamethylene diisocyanate) (PHMD), and hexamethylene diisocyanate (HDI), was developed for peripheral nerve recording and stimulation application.[47] This hydrogel can self-climb onto the peripheral nerves driven by body temperature, and matches the geometry of the peripheral nerve, thus avoiding the irreversible neural damage caused by complicated surgical implantation.

The biocompatibility, including nonimmunogenic responses and nontoxic side effects, of a conductive hydrogel is a stringent demand for bioelectronics in human health-related applications.[125] All the components in a conductive hydrogel need to meet the criteria of biocompatibility, including the polymer network, cross-linkers, conductive fillers, and their degradation products. However, this requirement often brings a dilemma in material selection. Natural polymers (e.g., gelatin, agarose, chitin, hyaluronic acid, and silk fibroin) are ideal building blocks for biocompatible hydrogels, but they suffer from a few drawbacks including poor conductivity and material processability. The optimization of natural polymers mainly relies on facile chemical modification or functional group grafting.[126,127] Such modifications may raise safety concerns due to the chemicals used and functional groups introduced in the process. On the other hand, synthetic polymers, such as PLA, PEG, and PEODT:PSS, provide controllable physical/chemical properties to the hydrogels, while their biocompatibility and bioactivity are typically lower than those of natural polymers. A further challenge of developing biocompatible conductive hydrogels is the integration of biocompatibility with other functions, such as good conductivity, high mechanical strength, and self-healing properties.

Silk fibroin (SF) is a widely used biomaterial for constructing conductive hydrogels (Figure 7a), owing to its good biocompatibility and biodegradability.[128−131] SF is composed of three parts: a heavy chain (~390 kDa), a light chain (~26 kDa), and a glycoprotein chain (~28 kDa). The heavy chain of the SF contains hydrophobic and hydrophilic domains (Figure 7b), forming the ordered crystalline and amorphous domains in the fibroin, respectively. The crystalline domain (β-sheet) can serve as physically crosslinking points of the hydrogel, thereby avoiding the addition of potentially hazardous chemical cross-linkers. The conductivity of SF hydrogels can be easily tuned by incorporating conductive fillers, such as carbon-based materials, metal nanomaterials, and conductive polymers into the hydrogel network (Figure 7c).[132,133] SF can also be combined with synthetic polymers to form hybrid hydrogels with desirable functions for various applications. For example, a hybrid of PAM and SF (PAM/SF) hydrogel showed tunable mechanical properties and excellent stretchability (600% strain). The conductivity of the hydrogel can be tuned by introducing GO and PEDOT:PSS into the PAM/SF hydrogel matrix.[134] A mixture of SF and PVA could form a hydrogel with improved stability and water absorption properties. Yang et al. developed a SF/PVA/Borax conductive hydrogel with high stretchable ability, self-healing properties, and strong adhesion to artificial skin.[135] Although SF could be used as a biocompatible and degradable substrate for hydrogel electronics, they still face challenges such as (1) biocompatible concerns introduced by conductive polymers and fillers, (2) rational structural design to achieve high elasticity without chemical modification, and (3) the integration of additional desired functions (e.g., adhesion to tissue/organs).

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Table 1. Examples of Multifunctional Conductive Hydrogels in Bioelectronics

hydrogel network	features	processing methods	application	ref
		tough and stretchable conductive hydrogels		
pure PEDOT:PSS	stretchability (>35% strain)	solvent annealing	bioelectronic devices	72
PEDOT:PSS/IL	conductivity (>4100 S/cm)	solution mixing and annealing	LED and FET devices	73
PANI/P-(AAm-*co*-HEMA)	stretchability (about 220% strain)	precursor reduction	strain sensors	74
PAAm/PANI	stretchability (626% strain)	in situ polymerization	strain sensors	44
MXene (Ti_3C_2Tx)-PVA	strain sensitivity (gauge factor: 25)	physical mixing	pressure/strain sensors	46
		self-healing and injectable conductive hydrogels		
PPy/alginate-gelatin	healed (In 40 min)	low-temperature fabrication (−20 °C)	repairable circuits	104
carrageenan/PAAm	strain sensitivity (gauge factor: 343)	solvent replacement and transfer	biosignal detection	106
Dex-AT/CECS	conductivity (10^{-2} mS/cm)	chemical modification	muscle regeneration	109
graphene/SF/Ca^{2+}	healed (100%) (In 3 s)	mask printing	strain/humidity sensor	133
		adhesive conductive hydrogels		
PEDOT:PSS/PU	adhesion strength (>120 kPa)	electrodeposition	conductive adhesives	116
PPy/SF	adhesion strength (>1.5 MPa)	interfacial polymerization	ECG signals monitoring	117
PDA/CNTs	adhesion strength (>50 KPa)	glycerol−water binary solvent	biosignal detection	45
		shape memory conductive hydrogels		
EVA/PCL/CNTs	triggering voltage (20 V)	physical mixing	electroactuator	122
PVA/catechol-Fe^{3+}	tensile strength (3.25 MPa)	freeze−thaw and solvent exchange	intelligent actuators	123
PCL/PHMD/HDI	elastic modulus (100 MPa to 300 kPa)	transfer printing	peripheral nerve stimulation	47
		biocompatible conductive hydrogels		
PAM-SF/GO-PEDOT:PSS	stretchability (600% strain)	physical mixing	strain/pressure sensors	134
SF-PVA/borax	stretchability (>5000% strain)	physical mixing	biocompatible sensing platform	135
PEDOT-based microelectrode	stretchability (>200% strain)	photolithography	implantable bioelectronics	49
PPy-PDA/gelatin-Fe^{3+}	conductivity (6.51×10^{-4} S/cm)	in situ polymerization	cardiac patches	50
PEDOT/PU	conductivity (120 S/cm)	electropolymerization	cell scaffold	150
		others functional conductive hydrogels		
chitosan/PANI	antibacterial hydrogel	chemical modification	wound healing	108
PAAm/alginate/$CaCl_2$	anti-freezing hydrogel	physical mixing	pressure sensors	140
PAM/cellulose-nano crystals/CNTs	anti-fatigue-fracture hydrogel	solution mixing	strain/pressure sensors	137

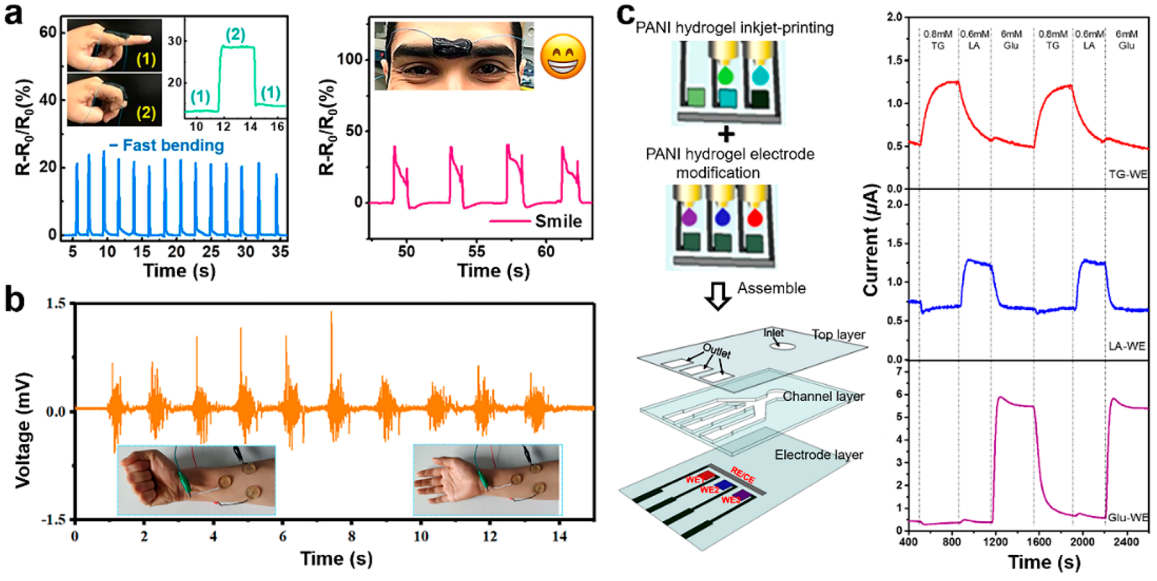

Figure 8. Wearable bioelectronics based on multifunctional conductive hydrogels. (a) Body motion detection using a PVA flexible conductive hydrogel sensor. [Reproduced with permission from ref 46. Copyright 2018 AAAS.] (b) Physiological signal detection using skin-attachable conductive hydrogel electrodes. [Reproduced with permission from ref 151. Copyright 2019 Elsevier.] (c) Multiplexed biomarks detection using PANI hydrogel based electrodes. [Reproduced with permission from ref 61. Copyright 2018 American Chemical Society.]

The properties of conductive hydrogels can be tailored for different applications.[136−138] For example, conductive hydrogels face the challenge of fatigue fracture under overload and exhaustion conditions, especially in the presence of severe mechanical damage. Developing anti-fatigue fracture conductive hydrogels can greatly improve the durability of the hydrogel-based electronics in long-term usage.[139] Under subzero temperature conditions, most conductive hydrogels

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inevitably lose their elasticity and conductivity because of the frozen aqueous solvent. To break this barrier, antifreezing conductive hydrogels have been explored.[140−143] Antibacterial conductive hydrogels have also been widely tested in wound healing.[108,144] All these examples demonstrate that to meet the actual needs of the practical applications is critical for the design and fabrication of a functional conductive hydrogel. Integrating versatile functions to one conductive hydrogel still remains a challenging task.[145−147]

APPLICATIONS AND CHALLENGES OF CONDUCTIVE HYDROGELS IN BIOELECTRONICS

Conductive hydrogel is an ideal building block for many wearable electronic devices for the monitoring of biophysical and biochemical markers of human body (Table 1).[148,149] Because of their capability of converting mechanical stimuli into electrical signals, conductive hydrogels can be used in fabricating pressure and strain sensors.[150] Sensors based on MXene (Ti_3C_2Tx)-PVA hydrogel effectively detected motion and subtle changes of a human body, and demonstrated high stretchability, conformable skin adhesion, and preferably self-healing properties (Figure 8a).[46] Multifunctional conductive hydrogels have also been used for making skin-attachable flexible electrodes for the detection of electrophysiological signals, including ECG, electromyography (EMG), and electroencephalography (EEG) signals (Figure 8b). Wang et al. reported skin-attachable PAA/PEDOT hydrogel electrodes that can detect physiological signals of ECG and EMG.[151] The proposed PAA/PEDOT hydrogel electrodes were sufficiently sensitive for noninvasive physiological signals detection. As

The biocompatibility and biodegradability of the hydrogels are essential to various in vivo applications, along with mechanical robustness and adhesion to biological tissues.

electrophysiological signals are typically weak, improving the conductivity and the signal-to-noise ratio (SNR) is the primary concern in the material design. Additionally, as the electrodes are directly attached to human body for continuous signal monitoring, skin adhesion, long-term stability, and biocompatibility are also important criteria for the design of the hydrogels.

Apart from biophysical sensors, conductive hydrogels have also been used in sensors for detecting biochemical markers. Li et al. reported biochemical sensors based on PANI hydrogel for the real-time detection of lactate, glucose, and triglycerides in human serum samples.[61] The PANI hydrogel precursor, platinum nanoparticles, and enzyme solutions (glucose oxidase, lactic oxidase, and lipase/glycerol kinase/L-α-glycerophosphate oxidase) were inkjet-printed on the designated electrodes one by one to form a multiplexed biosensor (Figure 8c). The hydrophilic porous structure of the PANI hydrogel increases the enzymatic reactivity and facilitates the transportation of metabolite molecules, thus improving the electrode's sensor sensitively.

Conductive hydrogels have also demonstrated great potential in implantable bioelectronics and tissue engineering

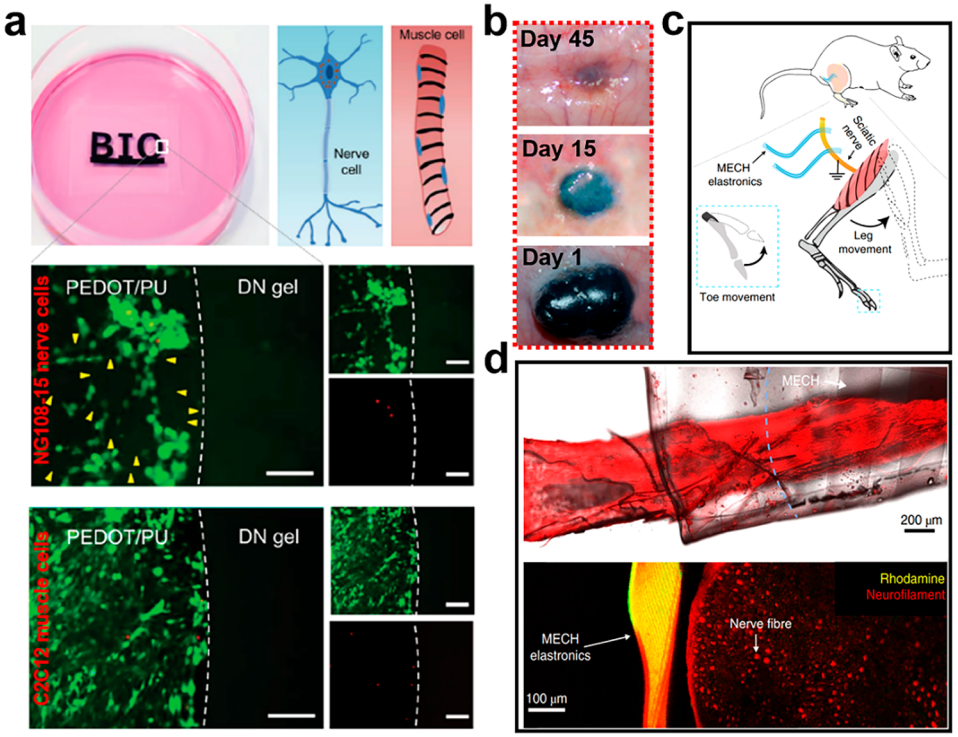

Figure 9. Tissues interface bioelectronics based on multifunctional conductive hydrogels. (a) Cell induction and differentiation based on PEDOT/PU conductive hydrogel. [Reproduced with permission from ref 152. Copyright 2014 Wiley-VCH.] The hydrogel showed good biocompatibility, stretchability, and conductivity. (b) Cardiac cell therapy based on degradable CS-AT conductive hydrogel. [Reproduced with permission from ref 153. Copyright 2016 American Chemical Society.] (c) Implantable bioelectronics based on PEDOT conductive hydrogel for localized low voltage neuromodulation in a mouse. (d) Images of the PEDOT-based microelectrode (MECH) wrapped around the mouse's sciatic nerve. [Reproduced with permission from ref 49. Copyright 2019 Nature Publishing Group.]

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(Table 1). The high-water content and porous structure of the hydrogel provide an extracellular matrix-like environment with matched mechanical properties to the tissue, giving conductive hydrogels significant advantages over traditional inorganic materials such as silicon and metals. The biocompatibility and biodegradability of the hydrogels are essential to various in vivo applications, along with mechanical robustness and adhesion to biological tissues.

The first reported PEDOT/PU conductive hydrogel exhibited good biocompatibility to both muscle and nerve cells (Figure 9a).[152] A degradable chitosan-*graft*-aniline tetramer (CS-AT) conductive hydrogel with self-healing and antibacterial activity was developed and used for cardiac cell therapy (Figure 9b).[153] Because of the early success of applying conductive hydrogels in tissue engineering, the potential of conductive hydrogels has been rapidly explored in various aspects of tissue engineering, such as nerve cell behavior regulation and wound healing,[49,154−156] as well as implantable bioelectronics for neurological signal detection.[49,157] Liu et al. reported a PEDOT-based implantable electronics for low-voltage neuromodulation (Figure 9c and d). The electronics can be used to electrically stimulate the sciatic nerve in a mouse and exhibit good stability and biocompatibility for long-term implantation.

CONCLUSIONS AND PERSPECTIVES

Many challenges still need to be addressed to fulfill the full potential of conductive hydrogels.[158,159] Currently, incorporating conductive polymers, carbon-based materials, and their derivatives into a nonconductive hydrogel matrix is still the dominate approach for formulating conductive hydrogels.[26,73,160] Conductive hydrogels formed by these traditional methods have good processability but often have unstable conductivity. One approach to improve the electrical conductivity is to synthesis single-component conductive hydrogels, thereby avoiding non-conductive network of the hydrogel matrix.[33,72] By adding crosslinking sites and biodegradable linkers to various conductive polymers, they can form single-component conductive hydrogels by in situ polymerization or self-assembly with significantly improved conductivity and bioactivity.[26,161]

The integration of conductive hydrogel with biological tissue is another challenge in the field. Inorganic bioelectronics often cause neuroinflammatory responses induced by chemical and mechanical mismatch between inorganic bioelectronics and biological tissues.[16,21] In strong contrast, hydrogel based bioelectronics show lower neuroinflammatory responses benefited from their similar mechanical property to that of biological tissue.[162] However, the electron current (or hole current in some cases) carried by hydrogel electronics have to be converted to ion current at electrode/biological tissue interfaces to stimulate the biological systems. This switching requires a high voltage (about 1 V in water) between the electrode/biological tissue interfaces, which can cause local heat effect, electrode degradation, and biocompatibility issues.[125] Ionic hydrogel electronics could avoid the current conversion at the electrode/tissue interfaces, and eliminate the associated adverse effects form the high converted voltage. However, ionic hydrogels often suffer from problems caused by ion diffusion.[163]

Despite the great progress over the past decade, conductive hydrogels are still in their infancy. Future attempts shall focus on (i) methods to improve and maintain stable conductivity and (ii) the robust integration of conductive hydrogels in bioelectronic devices. Apart from issues on the materials sides, we shall also pay more attentions to the biological interactions between bioelectronics and tissues, which are essential to the design of practical hydrogel electronics.

Biocompatible conductive hydrogels with self-healing, shape memory, and tissue adhesion properties are critical for the development of next generation bioelectronics. While high conductivity, mechanical robustness, and high stretchability are the basic requirements for most hydrogel-based electronics, many practical applications have called for the needs of developing conductive hydrogel with additional functionalities such as shape memory, self-healing, and tissue adhesiveness. For hydrogels operating at the tissue/cell interfaces, biocompatibility and biodegradability are also important concerns. It is critical to fabricate conductive hydrogels with tailored properties to meet the actual needs of different applications in the era of personalized healthcare.

Biocompatible conductive hydrogels with self-healing, shape memory, and tissue adhesion properties are critical for the development of next generation bioelectronics.

AUTHOR INFORMATION

Corresponding Authors

Hongbo Zeng − *Department of Chemical and Materials Engineering, University of Alberta, Edmonton, Alberta T6G 1H9, Canada;* orcid.org/0000-0002-1432-5979; Email: Hongbo.Zeng@ualberta.ca

Jing Yu − *School of Materials Science and Engineering, Nanyang Technological University, 639798, Singapore;* orcid.org/0000-0002-4288-951X; Email: yujing@ntu.edu.sg

Authors

Fanfan Fu − *School of Materials Science and Engineering, Nanyang Technological University, 639798, Singapore;* orcid.org/0000-0002-4443-9846

Jilei Wang − *School of Materials Science and Engineering, Nanyang Technological University, 639798, Singapore;* orcid.org/0000-0002-0950-0971

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmaterialslett.0c00309

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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