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REVIEW

Hydrogel-based soft bioelectronics for personalized healthcare

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Abstract

Soft bioelectronics have emerged as a promising platform for personalized healthcare, offering improved compatibility with biological tissues. Among various soft materials, hydrogels stand out due to their unique tissue-like properties and multifunctionality. However, the development of hydrogel-based bioelectronics faces three major challenges: (1) achieving a wide range of mechanical properties, from kilopascals to gigapascals, to match diverse tissues from soft brain to stiff tendon; (2) balancing and decoupling various material properties, particularly mechanical and electrical characteristics, and (3) achieving effective implantation and integration with target organs. This review provides a comprehensive overview of recent advancements in hydrogel-based bioelectronics, focusing on strategies to address these challenges. We first explore approaches to tune the mechanical properties of hydrogels, matching them with a wide range of tissues from soft brain tissue to stiff tendons. We then discuss innovative methods to incorporate conductivity into hydrogels while maintaining their mechanical integrity, highlighting recent developments in conductive polymers that show potential in decoupling electrical and mechanical properties. To address the challenge of implantation, we examine emerging concepts in stimuli-responsive hydrogels capable of programmable deformation, enabling targeted attachment and conformability to specific organs. We also categorize and analyze applications of hydrogel-based systems in both wearable and implantable devices, compiling the latest progress in hydrogel bioelectronics at the application level. While significant advancements have been made, integrating multiple functionalities within a single hydrogel-based device remains a considerable challenge. Further research is necessary to develop truly multimodal bioelectronic systems that can seamlessly interface with the human body, ultimately translating these promising technologies into clinical practice.

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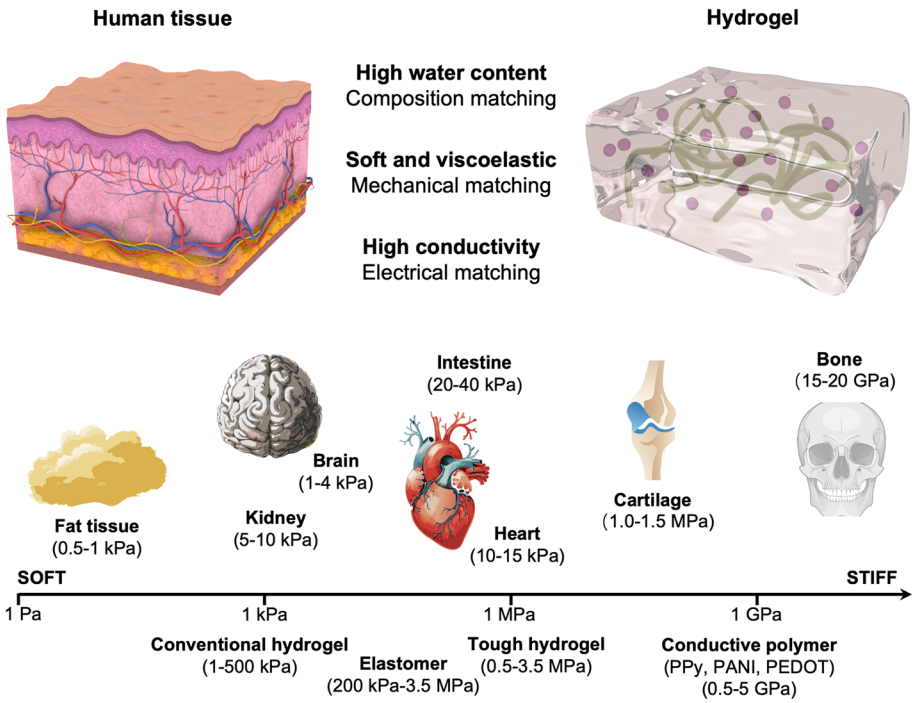
Graphical Abstract



Highlights

- Summarizes recent advances in hydrogel bioelectronics for personalized healthcare, focusing on mechanical, electrical, acoustic, and optogenetic coupling.
- Discusses the latest progress in conductive polymers, particularly PEDOT:PSS, and their potential in decoupling electrical and mechanical properties.
- Discusses the concept of stimuli-responsive hydrogels that enable programmable deformation for targeted attachment and conformability to specific organs.

Keywords Soft bioelectronics · Personalized healthcare · Conductive hydrogel · Hydrogel device

Introduction

Personalized healthcare tailors diagnostic, therapeutic, and preventive strategies to individual patients based on their genetic profile, lifestyle, and environment [1–3]. Current approaches often rely on conventional electronic devices, such as rigid silicon-based sensors or metallic electrodes, for monitoring and treatment. For instance, implantable cardiac pacemakers use titanium casings and metal lead wires. However, these rigid materials pose significant challenges due to their mechanical mismatch with soft biological tissues [4, 5]. The Young's moduli of silicon and metals (in the gigapascal range) are orders of magnitude higher than those of biological tissues (in the kilopascal range), leading to poor conformability, limited biocompatibility, and potential tissue damage. While reducing the thickness of rigid materials can improve flexibility, it does not fully address the modulus mismatch, resulting in interfacial stress, delamination, and compromised performance [6]. Bioelectronics offer a promising solution by developing wearable and implantable devices that can seamlessly interface with the human body, enabling real-time monitoring of physiological signals and targeted therapies for personalized healthcare [7–10]. Recent advancements in this field have led to the development of ultra-thin, stretchable electronic skins for continuous health monitoring, biodegradable and transient electronics for temporary implants, and neural interfaces with unprecedented resolution for brain-machine communication. These

innovations, coupled with progress in materials science and fabrication techniques, are pushing the boundaries of what's possible in personalized medicine and human–machine interfaces.

Developing intrinsically soft electronic materials that closely match the mechanical properties of biological tissues is crucial for advancing soft bioelectronics in personalized healthcare applications. Among the various soft materials, hydrogels have emerged as a promising candidate for personalized healthcare due to their unique properties that closely mimic biological tissues [11–14]. Based on three-dimensional polymeric networks capable of absorbing and retaining large amounts of water, it can behave soft and flexible with mechanical properties similar to living tissues [15, 16]. To quantitatively illustrate the mechanical advantages of hydrogels, consider that traditional bioelectronic materials like silicon and metals have Young's moduli in the range of 100–300 GPa, far exceeding that of soft biological tissues (0.1 kPa to 2 MPa). In contrast, hydrogels can be engineered with moduli ranging from 0.2 kPa to 1 MPa, closely matching various tissue types. Additionally, hydrogels offer superior stretchability (100–1000% strain) compared to rigid materials (< 5% strain), enabling the creation of mechanically compatible interfaces that maintain performance under physiological motions while minimizing tissue damage risks. This compatibility allows hydrogel-based devices to conform to the complex surfaces of the human body, ensuring stable and comfortable interfaces for long-term use. In the meantime, the high water content and porous structure of hydrogels facilitate the transport of nutrients, oxygen, and bioactive molecules, enhancing biocompatibility and minimizing adverse tissue reactions. Furthermore, hydrogels exhibit efficient transduction of biological signals because of their excellent electrical, acoustic, and optical properties, which can be engineered for bioelectronic applications. These advantages have established hydrogels as an ideal platform for developing soft bioelectronic interfaces for personalized healthcare, as widely supported in the existing literature [11, 17].

Despite their potential, several challenges remain in fully utilizing hydrogels for personalized healthcare applications. A primary challenge is balancing electrical and mechanical properties. High electrical conductivity is crucial for efficient signal transduction, but increasing conductive fillers or modifying hydrogel composition often compromises mechanical integrity and stretchability, while conductive polymers typically face issues of brittleness. Recent advancements in decoupling mechanical and electrical properties have shown promising solutions to this challenge [18, 19]. Beyond electrical properties, expanding the functionality of hydrogels for diverse bioelectronic applications is also crucial. In this regard, significant progress has been made in areas such as optogenetics and acoustic coupling, which offer new modalities for interfacing with biological tissues. However, comprehensive reviews of these developments and their integration with traditional bioelectronic approaches are lacking. Another key challenge is the implementation of hydrogel-based bioelectronics, which depends on targeted attachment and conformability to specific organs and tissues. While previous methods focused on hydrogel adhesion, recent developments in stimuli-responsive hydrogels have enabled programmable deformation and adaptation to complex tissue structures. This aspect is crucial for personalized healthcare and warrants further exploration [20, 21].

In this review, we address two fundamental challenges in hydrogel-based soft bioelectronics for personalized healthcare: balancing conductivity and mechanical properties, and achieving effective implementation on targeted organs. Our discussion begins with an examination of hydrogels' unique ability to mimic a wide range of biological tissues' mechanical properties. From this foundation, we explore strategies for fine-tuning hydrogels' mechanical properties, enabling precise matching with specific tissues. Recent advances in using hydrogels as interface materials with conductive components are then analyzed, followed by an introduction to methods for incorporating conductivity into hydrogels. Particular emphasis is placed on approaches that decouple mechanical and electrical properties, culminating in an analysis of synergistic strategies that optimize both aspects of performance. The review extends beyond electrical properties to encompass recent progress in hydrogel-based bioelectronics for acoustic coupling and optogenetics applications. Innovative stimuli-responsive hydrogels capable of programmed deformation are explored, showcasing their potential for conforming to complex tissue structures. The final section categorizes and analyzes specific applications of hydrogel-based systems in wearable and implantable devices, demonstrating their versatility in various personalized healthcare scenarios. By systematically addressing these challenges and reviewing key advancements, this comprehensive framework aims to facilitate the development of next-generation hydrogel-based bioelectronic devices, significantly advancing personalized healthcare solutions.

Strategies for tuning mechanical properties through network design

To ensure reliable and durable operation of hydrogel bioelectronics, it is crucial to achieve mechanical matching and adaptivity of hydrogels to various tissues and organs. The mechanical properties of hydrogels are primarily determined by their polymer network structures. Over the past two decades, significant progress has been made in developing strategies for tuning the mechanical properties of hydrogels through the design of their network architectures (Fig. 1a)

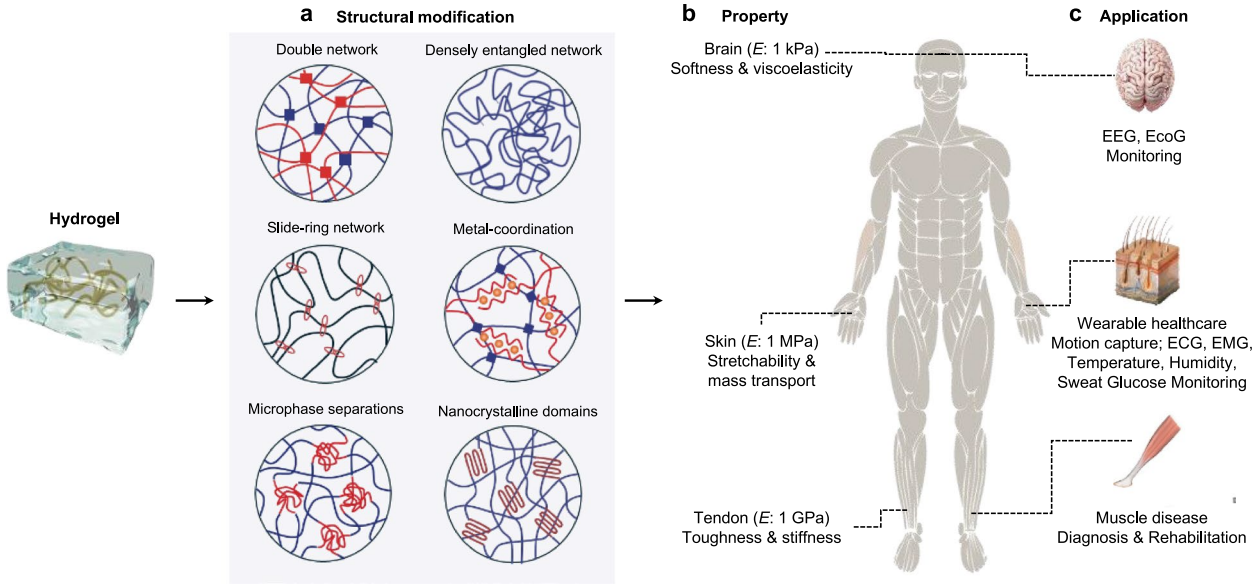


Fig. 1 Strategies for tuning the hydrogel properties and their applications in bioelectronics. **a** Network design strategies of hydrogels. **b** Mechanical properties of hydrogels matching different human tissues. **c** Applications of hydrogels with tailored properties in bioelectronics, including Electroencephalography (EEG), Electrocorticography (ECoG), Electrocardiography (ECG), and Electromyography (EMG)

[22–24]. Several key strategies have emerged, each offering unique advantages and challenges for tailoring hydrogel properties to specific bioelectronic applications. These strategies include designing double network (DN) structures, creating highly entangled networks, developing sliding ring networks, incorporating dynamic crosslinking mechanisms, and inducing microphase separation or nanocrystalline domains. The choice of strategy depends on the target tissue properties, desired functionality, and specific requirements of the bioelectronic device.

Designing double network (DN) structures is an effective approach to enhancing hydrogel toughness [25–29]. DN hydrogels comprise two interpenetrating polymer networks: a rigid, brittle first network that dissipates energy and a soft, ductile second network that sustains large deformation. This combination endows DN hydrogels with high strength and toughness, making them suitable for applications like artificial cartilage and tendon. Gong et al. first reported DN hydrogels in 2003, highlighting their excellent mechanical performance with high water content (~90 wt%), mechanical strength (1–10 MPa), and fracture toughness (100–1000 J m^{-2}) [29].

Another strategy involves densely entangled polymer networks with sparse chemical crosslinks [30, 31]. These entanglements enhance toughness, while sparse crosslinks maintain elasticity. Such hydrogels are promising for stretchable applications like epidermal electronics. However, stress relaxation over time is a concern. Suo and coworkers developed tough hydrogels with entangled polyacrylamide networks, achieving a fracture energy of 1000 J m^{-2} and a stretch limit of 10 times the original length [32].

Sliding ring hydrogels, composed of figure-of-eight crosslinks, enable large deformation without fracture due to mobile crosslinks distributing stress evenly [29–31, 33]. These hydrogels exhibit low hysteresis and self-reinforcing behavior, ideal for flexible electronics. However, their synthesis is complex. Ito and colleagues created polyrotaxane-based sliding ring hydrogels with a fracture stress of 5 MPa and a fracture strain of 1500% [34].

Incorporating dynamic metal-coordination interactions enhances mechanical strength and toughness, with reversible coordination bonds providing self-healing properties [35–38]. These hydrogels are promising for bioelectronic interfaces, though potential biotoxicity of metal ions needs evaluation. Zheng and coworkers synthesized tough, self-healing hydrogels with ferric ions, achieving a tensile strength of 1.2 MPa and a self-healing efficiency of 90% after 24 h [37].

Beyond the network design strategies discussed above, hydrogels with microphase-separated structures or nanocrystalline domains are particularly noteworthy in the context of bioelectronics applications [39–48]. These structures act as reinforcing fillers, providing effective energy dissipation mechanisms while enabling a wide range of mechanical properties through carefully controlled processing methods. This characteristic is especially valuable for bioelectronics applications.

Notably, the degree of microphase separation and formation of nanocrystalline regions can be simply controlled through various processing techniques. By employing ions and/or cosolvents, the porous structures of the hydrogel

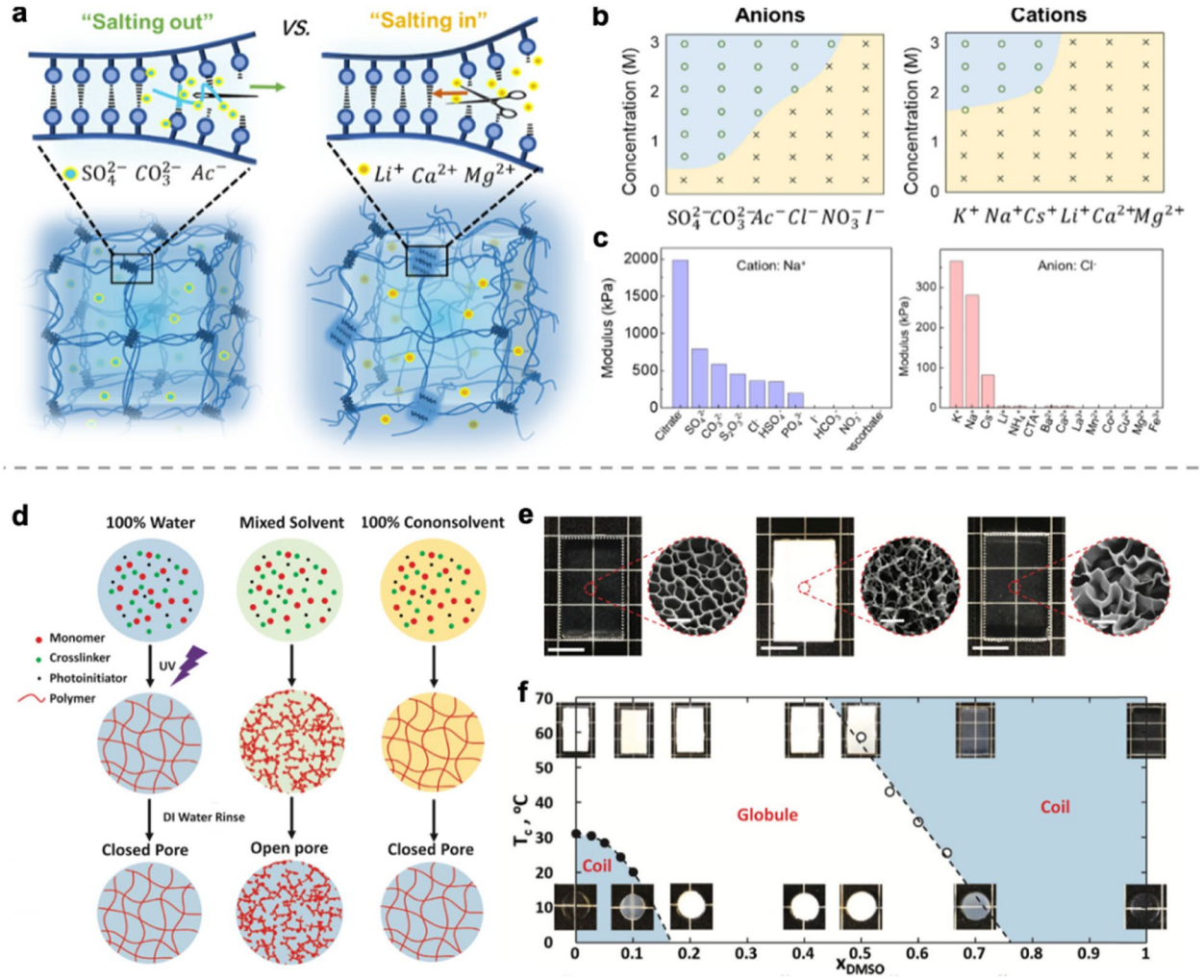


Fig. 2 Strategies for tuning the hydrogel properties through processing methods. **a-c** Hofmeister effect: **a** Illustration of "salting out" vs "salting in" effects. **b** Phase diagrams showing the influence of various anions and cations. **c** Modulus changes with different ions. Adapted with permission from [42]. **d-f** Cononsolvency effect: **d** Schematic showing pore structure changes in different solvent conditions. **e** Microscope images demonstrating structural changes. **f** Phase diagram illustrating the transition between coil and globule states as a function of DMSO concentration. Adapted with permission from [43]

polymer networks and consequently their mechanical and diffusive properties are effectively tuned across broad ranges. For instance, Wu et al. showed that by leveraging the Hofmeister effect, poly(vinyl alcohol) hydrogels could be engineered with a remarkably broad range of mechanical properties (Fig. 2a and b) [42]. Their study demonstrated tunable tensile strengths ranging from 0.1 to 28 MPa, and Young's moduli from 0.02 to 2000 MPa (Fig. 2c). This extensive range spans the mechanical properties of various human tissues, from soft brain tissue to stiff tendon, highlighting the potential for precise tissue-matching in bioelectronic applications [46, 49, 50]. The underlying principle of leveraging the Hofmeister effect has been adapted to various hydrogel compositions by carefully selecting ionic species and adjusting their concentrations [51–53]. Furthermore, Alsaid and Wu et al. has shown that by introducing cosolvents like dimethyl sulfoxide (DMSO) into the primary solvent water in the hydrogel precursor solutions, it is able to create hydrogels with controlled pore structures (Fig. 2d-f) [43, 54]. These structures can significantly impact mass transport properties, with some hydrogels showing up to a sixfold increase in deswelling rate compared to conventional hydrogels. The versatility of this method lies in its ability to create tailored microstructures without the need for complex chemical modifications [55]. Employing both ion- and solvent-assisted structure and property modulation methods, both mechanical and diffusive properties can be optimized, as demonstrated in highly ionically-conductive

tough hdyrogels useful for flexible energy storage devices and many others [56, 57]. Overall, this level of control over both mechanical and mass transport properties is crucial for applications such as drug delivery systems or biosensors in bioelectronic devices.

With such various structural modifications, it is crucial to consider the specific requirements of different human tissues and organs for bioelectronic materials, with the brain, skin, and tendons being key examples (Fig. 1b and c). For bioelectronic devices interfacing with the brain, an extremely low modulus of around 1 kPa is desired, which is challenging for other soft materials to achieve [11, 58]. Additionally, significant viscoelasticity is required to conform to the brain's complex surface structure. Tringides et al. developed a fully viscoelastic electrode array based on alginate hydrogels loaded with carbon nanomaterials, closely matching the mechanical properties of neural tissue [59]. The array could plastically deform to fit the brain cortex, showing promise in neural interface applications (Fig. 3a).

Regarding the skin, which requires modulus in the MPa range, hydrogels offer unique advantages over other soft materials [60–62]. While the skin's modulus range can be met by other materials, hydrogels provide mass transport capabilities due to their chemical composition and high water content [61, 63]. Cheng et al. reported an ultrathin polyacrylamide-alginate hydrogel film with high water vapor permeability, extreme mechanical compliance, and biocompatibility (Fig. 3b) [64]. This ultrathin hydrogel interface allows seamless integration of flexible electronic devices with the skin, promoting breathability and long-term wearability.

Finally, achieving the strength of tendons poses a significant challenge for hydrogels [65–67]. However, hydrogels with tendon-like properties hold immense potential in various applications. Sun et al. engineered a multifunctional tendon-mimetic hydrogel from an anisotropic assembly of aramid nanofiber composites (Fig. 3c) [67]. The hydrogel exhibited a high modulus of approximately 1.1 GPa, strength of around 72 MPa, and fracture toughness of 7333 J/m^2, closely matching natural tendons. The surfaces were functionalized with bioactive molecules to modulate cell behavior, and soft bioelectronic components were integrated for in situ sensing of physiological parameters. By designing polymer network structures with various strategies discussed before, hydrogels can be engineered to meet the diverse mechanical requirements of different human tissues. These advanced hydrogel-based materials show tremendous potential in bioelectronic applications, ranging from neural interfaces and skin-integrated devices to tendon-mimetic scaffolds with integrated sensing capabilities.

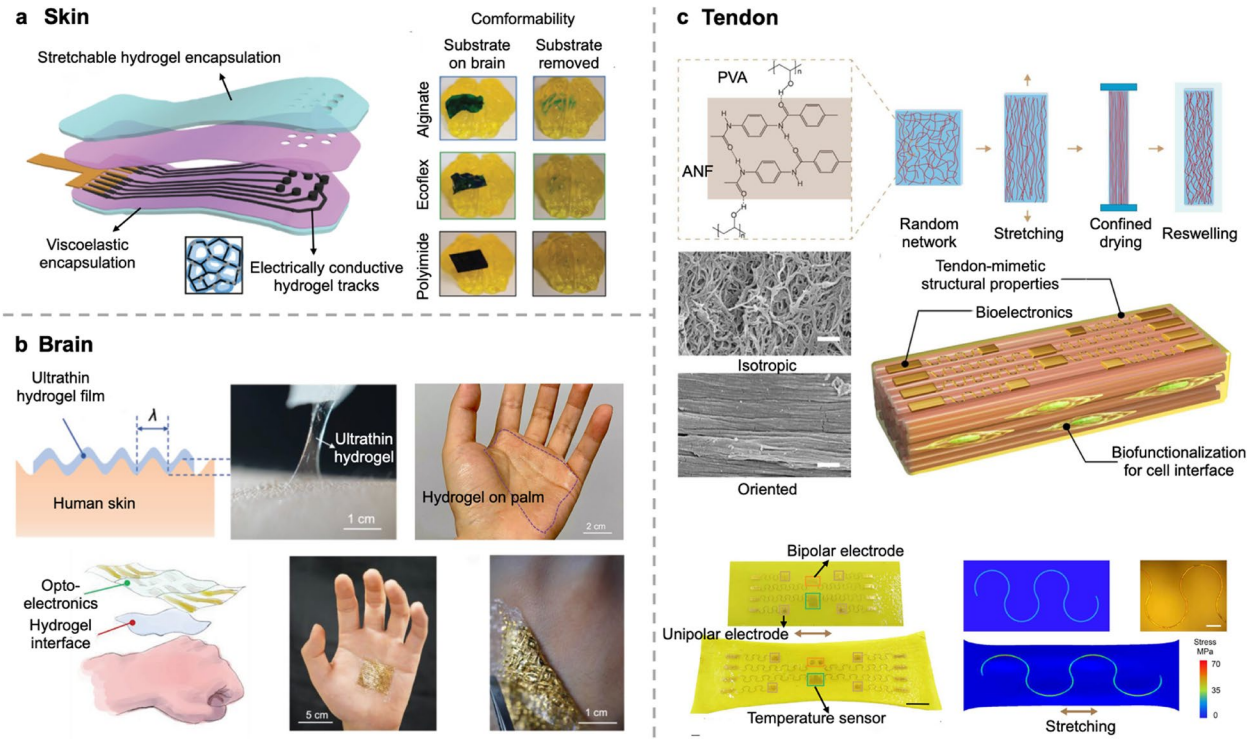


Fig. 3 Hydrogel-based bioelectronics for interfacing with different tissues. **a** Brain: Viscoelastic hydrogel-based electrode array for neural interfaces. Adapted with permission from [59]. **b** Skin: Ultrathin hydrogel film for epidermal electronics. Adapted with permission from [64]. **c** Tendon: Anisotropic aramid nanofiber (ANF) composite hydrogel mimicking tendon properties. Adapted with permission from [67]

Mechanical coupling through passive hydrogel interfaces

Hydrogels can serve as passive interfaces or substrates for fabricating conductive patterns to realize bioelectronic functionalities [68–71]. In this case, hydrogels primarily provide mechanical coupling without active conductive properties. The advantage of this approach is the ability to incorporate high-conductivity patterns or materials onto the hydrogel surface [71]. Patterning these conductive materials is a critical consideration in the design of such bioelectronic devices.

Lu et al. developed a cryogenic transfer method to pattern laser-induced graphene (LIG) onto an ultrathin adhesive polyvinyl alcohol-phytic acid-honey (PPH) hydrogel film (Fig. 4a) [72]. The low-temperature process enhances the interfacial bonding between the porous graphene and the crystallized water within the hydrogel. The PPH hydrogel layer serves as an energy dissipation interface and an out-of-plane electrical pathway, inducing deflected cracks in the LIG and significantly improving its intrinsic stretchability (Fig. 4b). This method allows for the fabrication of thin, soft, and stretchable LIG-hydrogel nanocomposites with high conductivity and mechanical compliance. On the other hand, Jiao et al. reported an in situ 3D printing method for fabricating liquid metal (LM)-hydrogel hybrids (Fig. 4c) [73]. The hydrogel matrix, composed of gelatin, sodium alginate, and potassium chloride, acts as a supportive medium for printing LM patterns. This method enables the direct integration of stretchable and conductive LM into the soft hydrogel, resulting in a mechanically compliant bioelectronic interface (Fig. 4d). Due to the wetting and alloying properties of LM, these LM-hydrogel hybrids demonstrate excellent electrical interconnection with conventional electronic components. Furthermore, the LM-hydrogel hybrids can be directly used as functional electronic devices without additional encapsulation or assembly processes for EMG and ECG monitoring (Fig. 4e).

This kind of approach demonstrates the potential of hydrogel-based bioelectronics, where hydrogels primarily serve as passive mechanical interfaces. The main advantage is the ability to incorporate highly conductive materials. However, there are also some limitations to consider, such as the long-term stability of the conductive patterns

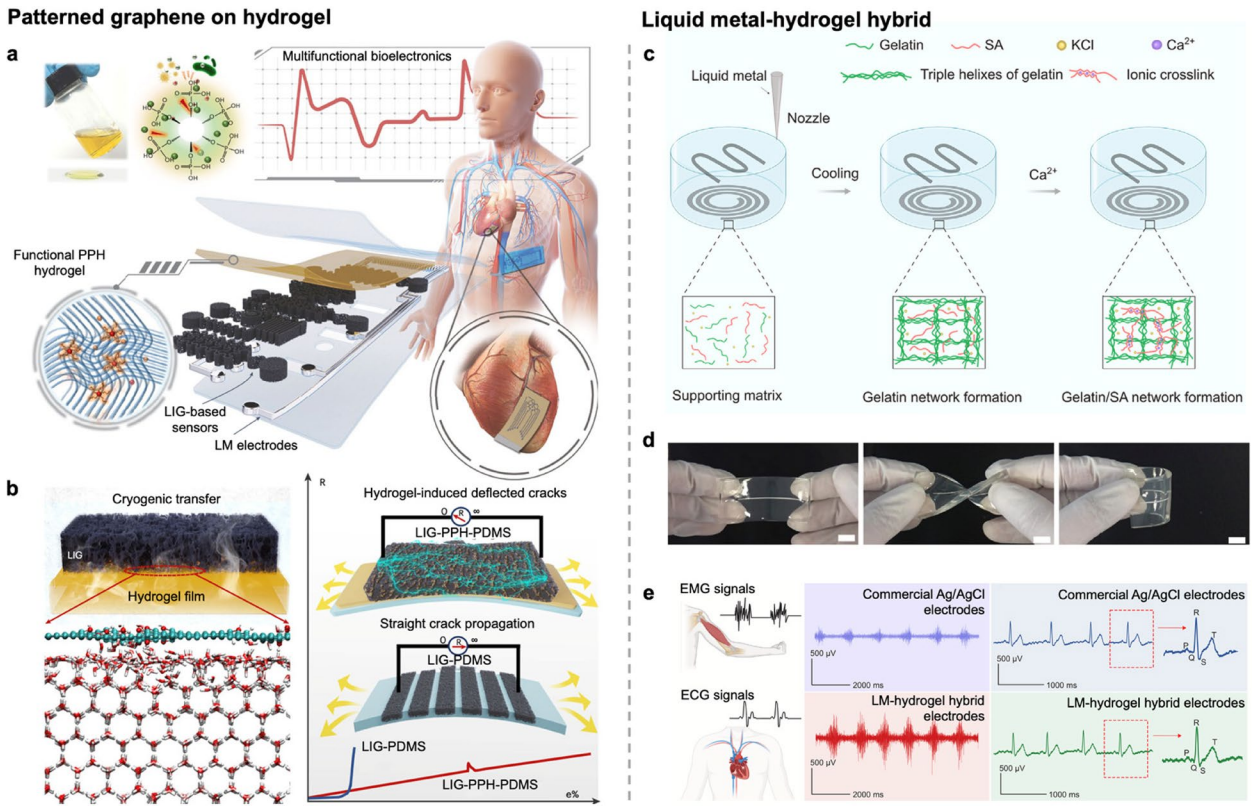


Fig. 4 Hydrogel-based bioelectronic interfaces using conductive patterns. **a-b** Patterned graphene on hydrogel: **a** Schematic illustration of a multifunctional bioelectronic device with laser-induced graphene patterned on a functional PVA-phytic acid-honey hydrogel **b** Cryogenic transfer method for patterning LIG on hydrogel. Adapted with permission from [72]. **c-e** Liquid metal-hydrogel hybrid: **c** Fabrication process of the hybrid. **d** Stretching stability of the liquid metal-hydrogel hybrid. **e** EMG and ECG signals recorded using the liquid metal-hydrogel hybrid electrodes. Adapted with permission from [73]

under repeated mechanical deformation and the potential delamination of the patterns from the hydrogel surface.

Strategies to impart conductivity to hydrogels

Following the discussion on mechanical coupling, we introduce several methods for incorporating conductivity in hydrogel-based systems [16, 74, 75]. Hydrogels can be engineered to achieve electrical coupling with biological tissues, enabling efficient transduction of biological signals. The strategies to impart conductivity to hydrogels can be broadly categorized into three types: (1) introducing ionic conductivity, (2) incorporating conductive fillers, and (3) fabricating conductive polymer hydrogels (Fig. 5a). Each approach has its advantages and limitations when applied in bioelectronics, which will be discussed in detail.

Ionic conductive hydrogels are obtained by introducing free ions, such as K^+, Na^+, Li^+, Al^{3+}, Fe^{3+}, ionic liquids, or polyelectrolytes, into the hydrogel network (Fig. 5b) [15, 76]. The high water content and porous structure of hydrogels facilitate the transport and diffusion of these ions, resulting in ionic conductivity. Ionic conductive hydrogels offer several advantages, including high transparency, good biocompatibility, and the ability to mimic the ionic environment of biological tissues. However, the conductivity of ionic hydrogels is generally lower compared to electronic conductive hydrogels, and the leakage of ions in aqueous environments may affect the long-term stability of the devices. Although ionic conductivity closely mimics the body's own electrical conduction mechanisms, ionic conductive hydrogels often face a trade-off between mechanical properties and ionic conductivity. Strong mechanical properties usually mean a denser network, which can restrict ion migration.

Conductive fillers, such as metal nanoparticles and carbon-based nanomaterials (graphene, carbon nanotubes), can be incorporated into hydrogels to endow them with electronic conductivity (Fig. 5c) [77–79]. These fillers form a conductive network within the hydrogel matrix, allowing for efficient electron transport. Conductive filler-based hydrogels exhibit high conductivity and good mechanical properties, making them suitable for various bioelectronic applications. Nevertheless, the incorporation of conductive fillers may compromise the biocompatibility of the hydrogels, and achieving a homogeneous dispersion of the fillers can be challenging.

Conductive polymer hydrogels are prepared by polymerizing conductive polymers, such as polypyrrole (PPy), poly(3,4-ethylenedioxythiophene) (PEDOT), and polyaniline (PANI), as shown in Fig. 5d [61, 80, 81]. These hydrogels possess inherent electronic conductivity due to the conjugated backbone of the conductive polymers. Conductive polymer hydrogels offer the advantages of high conductivity,

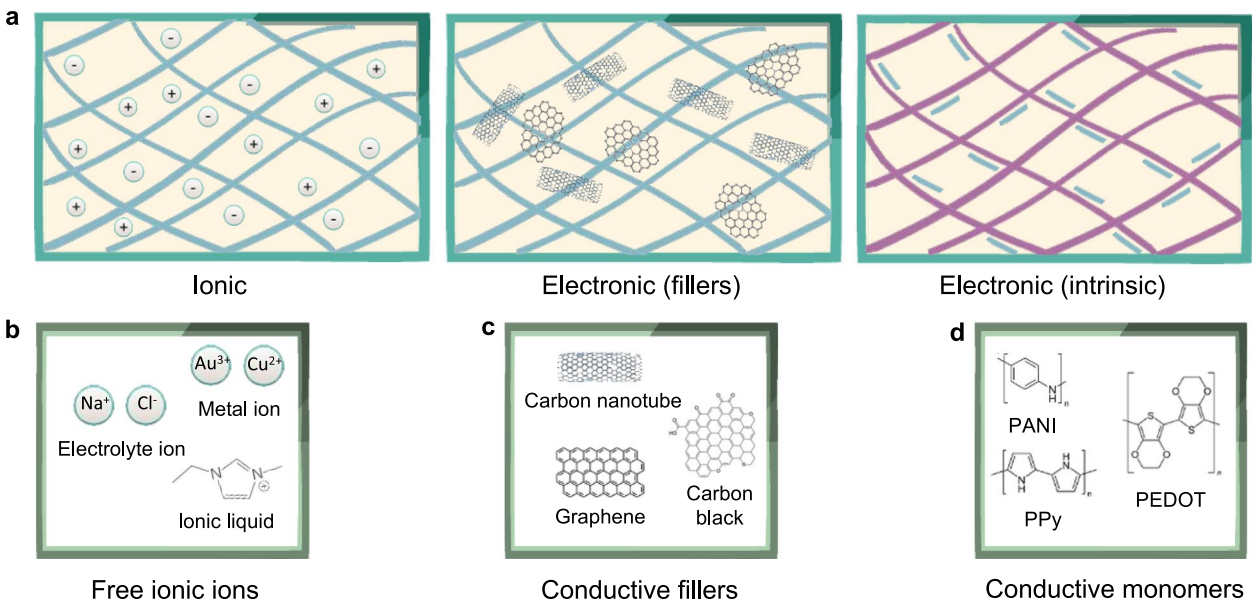


Fig. 5 Strategies for imparting conductivity to hydrogels. **a** Schematic representations of three main approaches to create conductive hydrogels: ionic conductivity, electronic conductivity through fillers, and intrinsic electronic conductivity. **b** Free ionic ions: Examples of electrolyte ions (Na^+, Cl^-), metal ions (Au^{3+}, $Cu.^{2+}$), and ionic liquids. **c** Conductive fillers: Illustrations of carbon-based nanomaterials such as carbon nanotubes, graphene, and carbon black. **d** Conductive monomers: Chemical structures of conductive polymers including polyaniline (PANI), polypyrrole (PPy), and poly(3,4-ethylenedioxythiophene) (PEDOT)

good biocompatibility, and the ability to tune their properties precisely by selecting monomers and polymerization conditions. However, the brittle nature of some conductive polymers may affect the mechanical properties of the hydrogels, and the long-term stability of these materials in physiological environments needs to be carefully evaluated.

When selecting a strategy to impart conductivity to hydrogels for bioelectronic applications, several factors should be considered, including the desired conductivity range, biocompatibility requirements, mechanical properties, and the specific application scenario. Ionic conductive hydrogels are particularly suitable for applications that require high transparency and ionic interfaces, such as ion-based stimulation devices. Conductive filler-based hydrogels are advantageous for applications demanding high conductivity and good mechanical properties, such as strain sensors. Conductive polymer hydrogels are promising for applications that require high conductivity and biocompatibility, such as implantable hydrogel devices.

Synergistic coupling of mechanical and electrical properties

Despite the promising potential of hydrogels in achieving effective coupling with biological tissues both mechanically and electrically, their synergistic integration remains a significant challenge to realize. For ionically conductive hydrogels, there is often a trade-off between high ionic conductivity and mechanical performance. Recent strategies have emerged to address this issue. Wang et al. developed a strong, tough, ionic conductive, and freezing-tolerant hydrogel by incorporating bentonite (BT) nanoplatelets into a cellulose matrix [82]. The strong cellulose-BT coordination and the ion regulation of the nanoconfined cellulose-BT structure enhanced mechanical strength and ionic conductivity (Fig. 6a), where BT nanoplatelets provided a direct path for ion transport. The hydrogel exhibited compressive strength up to 3.2 MPa, fracture energy up to 0.45 MJ m^{-3}, and ionic conductivities of 89.9 and 25.8 mS cm^{-1} at 25 °C and -20 °C, respectively (Fig. 6b). Another approach by Wang et al. designed a fatigue-free, fully healable hybrid ionic skin with a high-energy, self-healable elastic nanomesh [83]. Inspired by the repairable nanofibrous structure of human skin, they embedded a self-healable polyurethane (PU) nanomesh into a soft ionic matrix (Fig. 6c). This hybrid design decoupled mechanical and electrical properties by providing a resilient structure that can endure repeated deformation. The tension-induced alignment of nanofibers allowed the ionic matrix to breathe moisture, achieving a strain-sensing gauge factor of 66.8. This design achieved a fracture energy of 16.3 kJ m^{-2} and a fatigue threshold of 2950 J m^{-2} while maintaining skin-like self-healability,

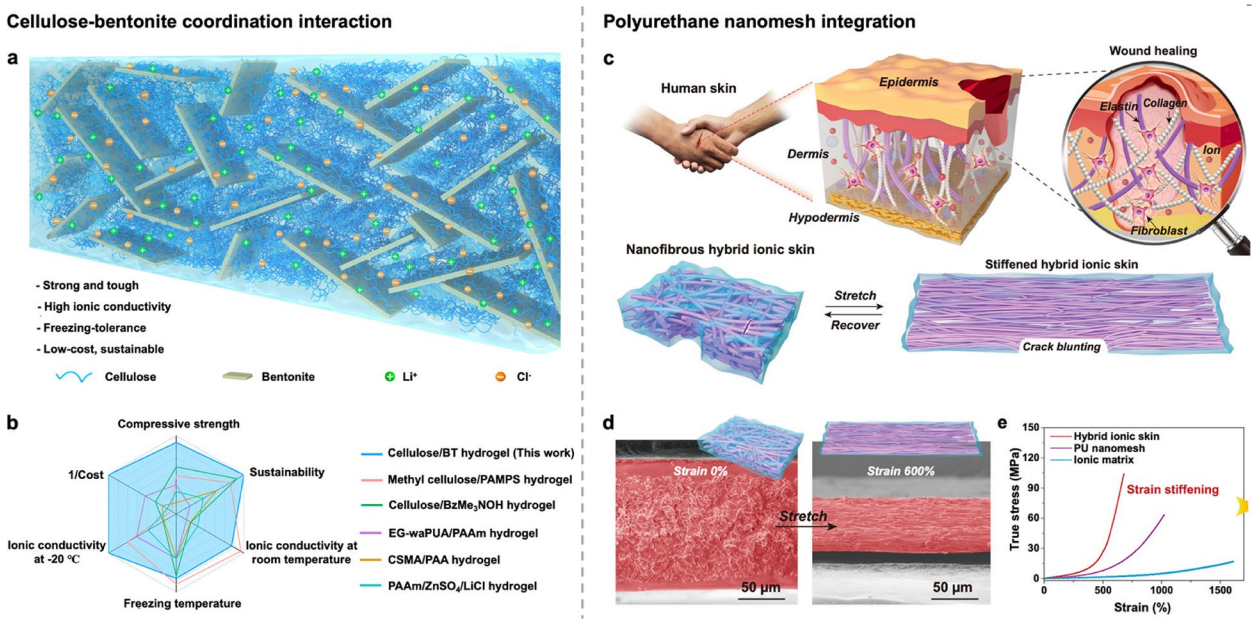


Fig. 6 Strategies for enhancing mechanical and electrical properties of ionic conductive hydrogels. **a-b** Cellulose-bentonite coordination interaction: **a** Schematic illustration of the cellulose-bentonite hydrogel structure. **b** Radar chart comparing various properties of the cellulose/BT hydrogel with other hydrogels. Adapted with permission from [82]. **c-e** Polyurethane nanomesh integration: **c** Illustration of the nanofibrous hybrid ionic skin. **d** Images of the hybrid ionic skin under different strain conditions. **e** Stress–strain curve comparing the hybrid ionic skin with its components. Adapted with permission from [83]

softness, stretchability, and strain-stiffening response (Fig. 6d and e). These studies show that incorporating secondary networks or nanostructures can achieve both high mechanical robustness and ionic conductivity in hydrogels by carefully designing component interactions and synergy.

For conductive polymers, the trade-off between mechanical and electrical properties is even more challenging. High conductivity often comes at the cost of brittleness and poor mechanical performance. To address this issue, several strategies have been proposed. For conductive polymers like polypyrrole (PPy) and polyaniline (PANi), strategies for synergistically improving mechanical properties and conductivity include hierarchical structuring, alignment of polymer chains, controlled nanoaggregation, and the creation of interpenetrating networks with flexible polymers. For instance, Zhao et al. developed a novel ice-templated low-temperature polymerization (ITLP) method to create a hierarchically structured, stretchable conductive hydrogel [84]. This approach successfully addressed the issue of nanoaggregation commonly observed in conventionally synthesized conductive hydrogels. The resulting PANi/PVA hydrogel exhibited a remarkable 29-fold increase in mechanical toughness and an 83-fold improvement in electrical conductivity, reaching 55.5 mS/cm, compared to traditional methods. This material demonstrated excellent sensing capabilities, able to simultaneously monitor large-scale human motions and minute physiological signals, showcasing its potential in health monitoring applications. In another study, Zhao et al. created a wood-inspired flexible all-solid-state hydrogel supercapacitor by morphologically tuning an aligned polyacrylamide (PAAm) hydrogel matrix [85]. The key to this approach was the creation of a highly oriented microchannel structure with tunable channel widths ranging from 47 to 12 μm, achieved through an ice-templating method and the addition of PVA to control pore size. This structure provided mechanical flexibility (0°–180° bending) while allowing uniform loading of PPy electrode material up to 7 mm thick. The PPy was embedded into the aligned PAAm aerogel matrix using vapor-phase deposition. The oriented microchannel structure reduced the tortuosity for ion transport while providing sufficient surface area for electrode material loading. When assembled with a PVA/LiCl electrolyte and a cellulose-based separator, this structural design resulted in an areal capacitance as high as 831 mF cm^{-2}, which was more than 4 times that of a non-aligned matrix.

In recent years, significant progress has been made in improving the properties of PEDOT:PSS. Research has focused on two main approaches: synergistically enhancing both mechanical and electrical properties, and decoupling the typically interdependent mechanical and electrical characteristics. These strategies have aimed to overcome the inherent limitations of PEDOT:PSS, such as its brittleness and the trade-off between conductivity and stretchability. The electrical conductivity of PEDOT:PSS is intimately linked to its polymer chain conformation and doping level. In its pristine state, PEDOT chains adopt a coiled conformation, limiting charge transport. Higher doping levels with PSS increase charge carrier density but can also lead to more coiled conformations due to electrostatic interactions. The key to enhancing conductivity lies in promoting an extended or linear chain conformation while maintaining high doping levels. This can be achieved through secondary dopants or processing techniques that induce phase separation between PEDOT and PSS, allowing PEDOT chains to align and form more efficient charge transport pathways. The balance between chain alignment and doping level is critical, as it determines the ease of charge hopping between chains and along the polymer backbone, directly influencing the material's overall conductivity.

Yao et al. developed a general strategy to ameliorate these issues by introducing a conducting polymer hydrogel with ultrahigh strength and conductivity with a capacitive behavior (Fig. 7a) [86]. The key to their success was forming a nanoporous conductive matrix with π-π interactions as both cross-linking sites and electron-transfer pathways, created through surface gelation coupled with chemical treatment and controlled densification. This strategy significantly decreased the low-frequency impedance and improved signal fidelity without affecting its high-frequency response. Jiang et al. took a different approach by developing a molecular engineering strategy based on a topological supramolecular network, which allows for the decoupling of competing effects from multiple molecular building blocks to meet complex requirements (Fig. 7b) [87]. By incorporating a single supramolecular crosslinker with tailored chemistry and topology, they achieved simultaneously high conductivity and crack-onset strain in a physiological environment, with direct photopatternability down to the cellular scale. The sliding cyclodextrin units in the polyrotaxane structure prevented the crystallization of polyethylene glycol (PEG) and provided better stretchability while maintaining high conductivity.

Lu et al. demonstrated that by designing interconnected networks of PEDOT:PSS nanofibrils, high-performance pure PEDOT:PSS hydrogels could be produced using a simple yet effective method (Fig. 7c) [88]. This method involves mixing the volatile additive dimethyl sulfoxide (DMSO) into aqueous PEDOT:PSS solutions, followed by controlled dry-annealing and rehydration. The resultant hydrogels exhibit a set of properties highly desirable for bioelectronic applications, including high electrical conductivity (~ 20 S cm^{-1} in PBS, ~ 40 S cm^{-1} in deionized water), high stretchability (> 35% strain), low Young's modulus (~ 2 MPa), superior mechanical, electrical, and electrochemical stability, and tunable isotropic/anisotropic swelling in wet physiological

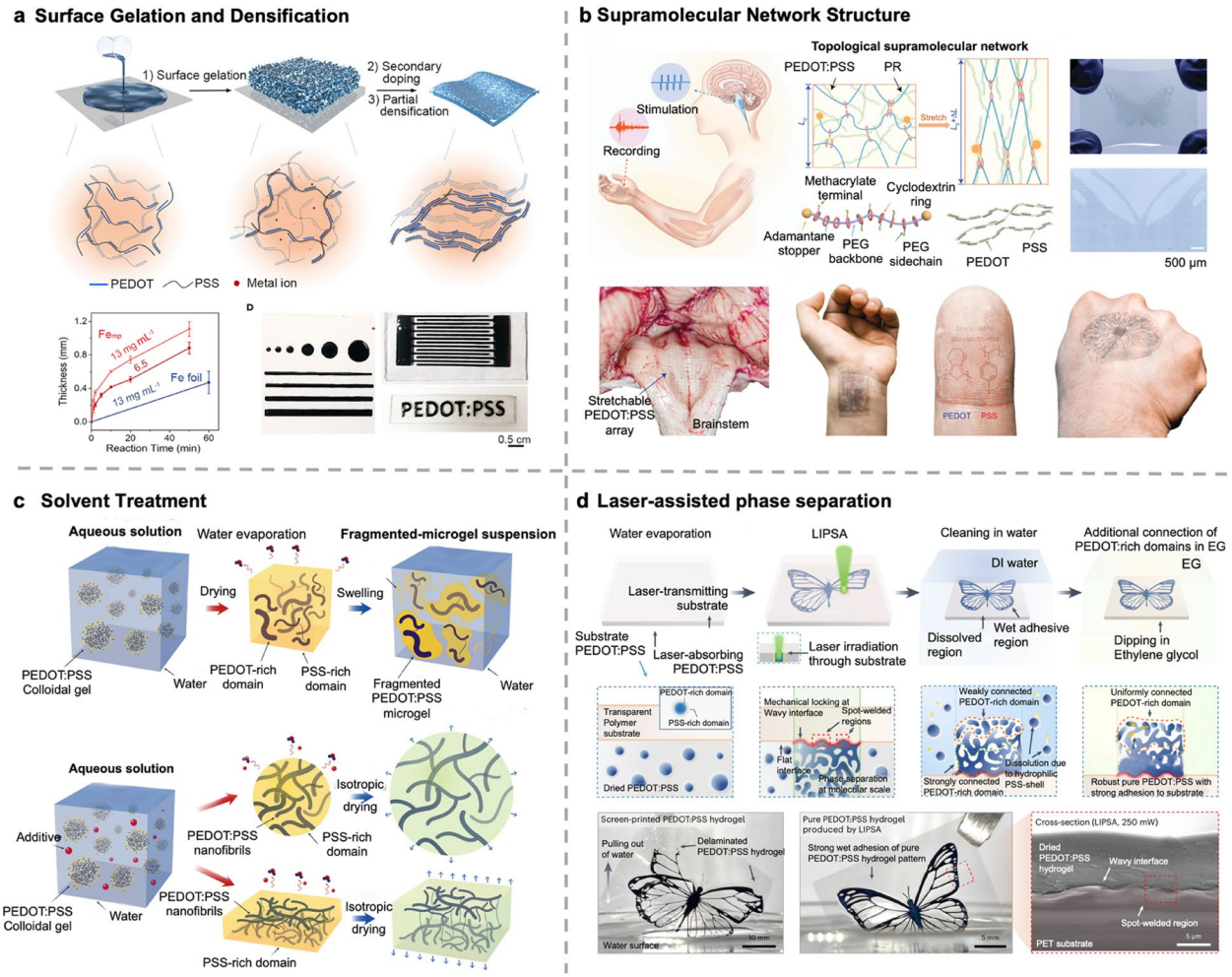


Fig. 7 Strategies for enhancing the mechanical and electrical properties of conductive polymer hydrogels. **a** Surface gelation and densification approach: Schematic illustration of the fabrication process involving surface gelation, secondary doping, and partial densification. Adapted with permission from [86]. **b** Supramolecular network structure: Illustration of the topological supramolecular network design, incorporating PEDOT:PSS, PEG, and cyclodextrin. Adapted with permission from [87]. **c** Solvent treatment method: Schematic representation of the PEDOT:PSS nanofibrils formation process using DMSO treatment, followed by dry-annealing and rehydration.Adapted with permission from [88]. **d** Laser-assisted phase separation: Illustration of the LIPSA process for creating pure PEDOT:PSS hydrogels, showing the steps of laser irradiation, phase separation, and additional crosslinking. Adapted with permission from [89]

environments. The PEDOT:PSS nanofibril network formed through this method provided mechanical robustness and efficient electron transport pathways. Won et al. developed a laser-induced phase separation and adhesion (LIPSA) method to create pure PEDOT:PSS conductive hydrogels with high stability and strong wet adhesion to various polymer substrates (Fig. 7d) [89]. Laser irradiation caused partial phase separation in the PEDOT:PSS and the formation of micro- and nanoscale interlockings at the interface, which significantly enhanced mechanical stability and adhesion strength. The hydrogel was further strengthened by post-treatment with ethylene glycol (EG). The resulting pure PEDOT:PSS hydrogels exhibited excellent mechanical stability and conductivity in wet conditions, including a conductivity of up to 101.4 S cm^{-1}.

Building upon the strategies discussed for addressing the trade-off between mechanical and electrical properties in conductive hydrogels, an emerging approach is to develop all-hydrogel bioelectronic devices [90–94]. In this design, both the matrix and the conductive components are composed of hydrogels, effectively decoupling the conflict between electrical conductivity and flexibility encountered in conventional conductive polymers. By employing hydrogels for the entire device, it becomes possible to achieve a synergistic coupling of mechanical and electrical properties that closely match those of biological tissues. Recent advancements in this field have demonstrated the feasibility and potential of all-hydrogel bioelectronic devices. Zhou et al. reported a bi-continuous conducting polymer hydrogel (BC-CPH) that simultaneously achieves high electrical

conductivity (over 11 S cm^{-1}), stretchability (over 400%), and fracture toughness (over 3,300 J m^{-2}) in physiological environments [91]. The BC-CPH was prepared by a phase separation process involving PEDOT:PSS as the electrical phase and hydrophilic polyurethane as the mechanical phase (Fig. 8a). This unique design allows for the formation of a percolated network of the electrical phase while maintaining a continuous mechanical phase, resulting in excellent electrical and mechanical properties. Furthermore, the BC-CPH was found to be readily applicable to advanced fabrication methods such as 3D printing, enabling the creation of complex and customizable all-hydrogel bioelectronic interfaces.

In another study, Hui et al. developed a 3D printing approach for fabricating soft hydrogel electronics using a curable hydrogel-based supporting matrix and a stretchable silver-hydrogel ink (Fig. 8b) [95]. The supporting matrix exhibits a yield stress fluid behavior, allowing for the precise patterning of the conductive ink within the matrix. After printing, the entire device can be cured to form a monolithic hydrogel with embedded circuitry. The resulting hydrogel electronics possess tissue-like softness (Young's modulus < 5 kPa) and stretchability (elongation ~ 18%) while the conductive ink maintains a high conductivity of around 1.4×10^3 S cm^{-1}. This 3D printing technique enables the fabrication of various functional hydrogel electronic devices, including strain sensors, inductors, and biological electrodes. The all-hydrogel bioelectronic devices showcased in these studies offer a promising platform for achieving a synergistic coupling of mechanical and electrical properties that mimic those of biological tissues. Moreover, the ability to fabricate complex 3D structures through advanced manufacturing techniques further expands the potential applications of all-hydrogel bioelectronics in personalized healthcare.

Acoustic and optical coupling of hydrogels with biological tissues

Beyond the previously discussed mechanical and electrical coupling, hydrogels can also be engineered to achieve acoustic and optical coupling with biological tissues [92, 93], thereby expanding their functionality in bioelectronics. Acoustic waves, generated by stimulating vibrations through electrical signals and converting the reflected sound waves back into electrical signals, enable the collection of biological information and are considered a part of bioelectronics. Similarly, optogenetics, which involves the use of light stimulation to control and manipulate bioelectrical signals within the body, also expand the domain of bioelectronics [18, 96–98].

Recent advancements in hydrogel-based materials have shown promising results in acoustic coupling with biological tissues. Hydrogel-based materials have been utilized to fabricate high-performance ultrasonic transducers. Wang et al. reported a transparent and stretchable ionic hydrogel-based ultrasonic transducer that can conform to complex surfaces and generate high-intensity focused ultrasound (Fig. 9a)

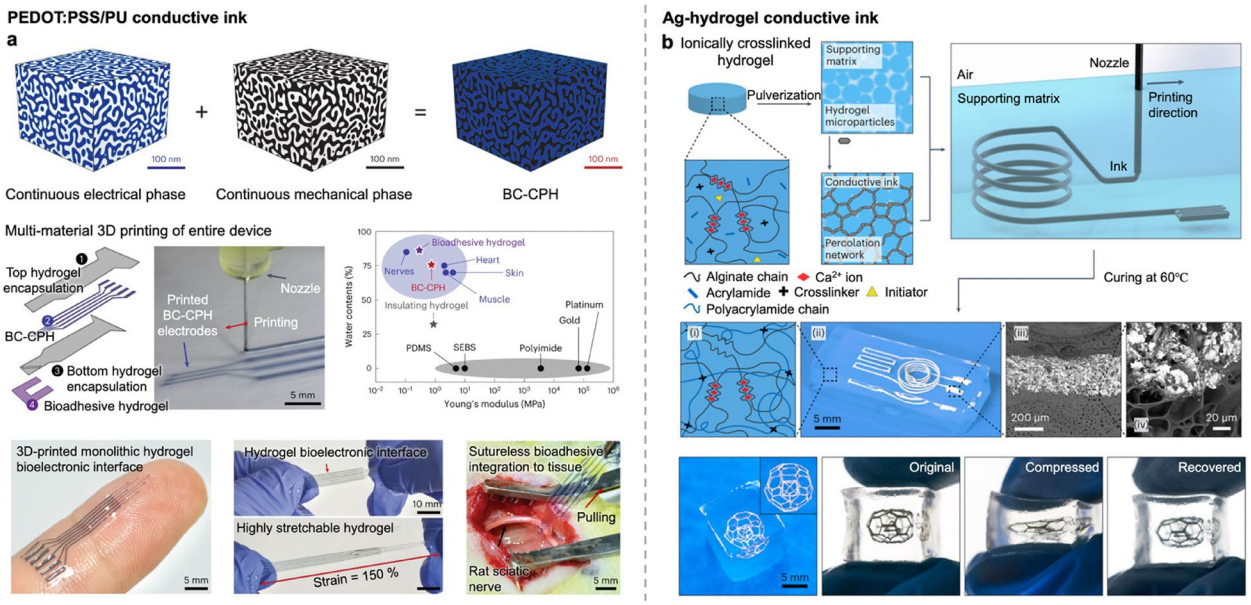


Fig. 8 All-hydrogel bioelectronic devices fabricated through advanced manufacturing techniques. **a** PEDOT:PSS/PU conductive ink: Illustration of the bi-continuous conducting polymer hydrogel (BC-CPH) structure, combining the electrical phase (PEDOT:PSS) and the mechanical phase (polyurethane). Images show the multi-material 3D printing process for creating soft electronic devices, the conformability of the printed hydrogel to skin, and its integration with biological tissues. Adapted with permission from [91]. **b** Ag-hydrogel conductive ink: Schematic illustration of the 3D printing process using a supporting matrix and conductive ink. Adapted with permission from [95]

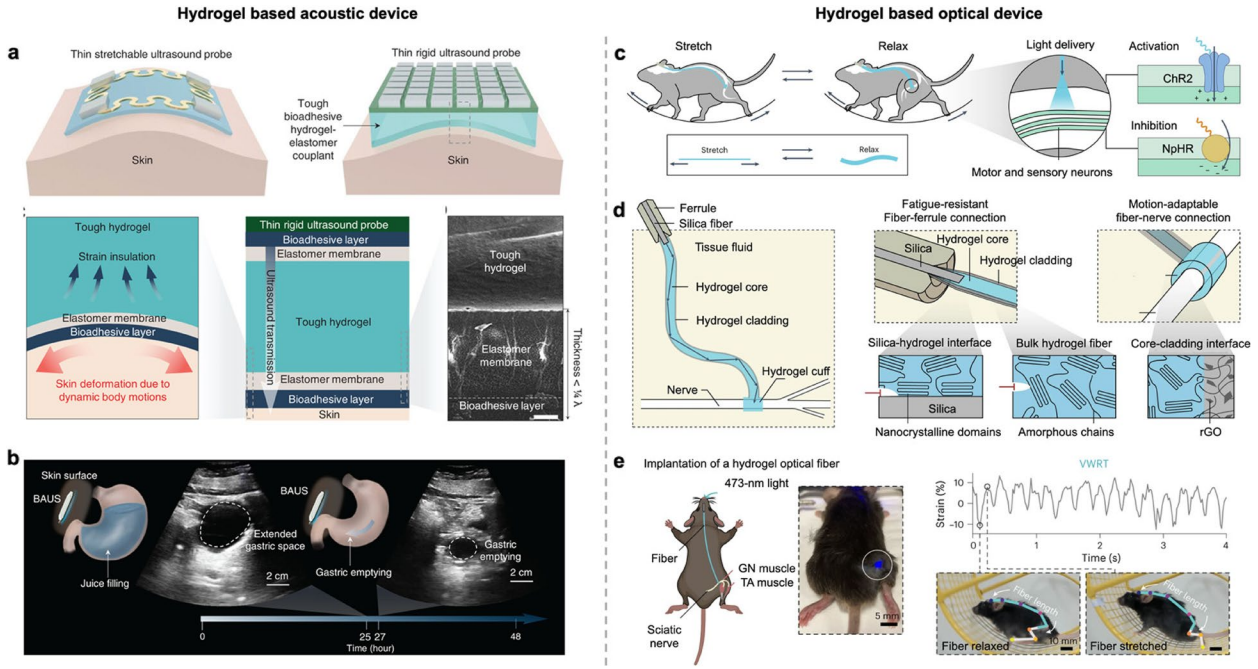


Fig. 9 Acoustic and optical coupling of hydrogels with biological tissues. **a, b** Hydrogel-based acoustic device: **a** Schematic comparison of thin stretchable and thin rigid ultrasound probes, highlighting the superior conformability of the hydrogel-based probe to skin. Scale bar is 10 μm. **b** Ultrasound images demonstrating the imaging capability of the hydrogel-based probe over time. Adapted with permission from [99]. **c-e**Hydrogel-based optical device: **c** Illustration of the implantation and light delivery process using a hydrogel optical fiber in a mouse model. **d** Detailed structure of the hydrogel optical fiber, showing its core-cladding design and the mechanism of light transmission. **e** Demonstration of the hydrogel optical fiber's functionality, including implantation images, light transmission through the fiber, and its performance under stretching conditions. Adapted with permission from [19]

[99]. The hydrogel transducer, composed of a polyacrylamide-lithium chloride hydrogel, exhibited excellent acoustic impedance matching with biological tissues, high transparency, and a wide frequency bandwidth (Fig. 9b). This technology holds promise for various biomedical applications, such as ultrasound imaging, therapy, and neuromodulation.

Related to optogenetics, Liu et al. developed a fatigue-resistant hydrogel optical fiber that can deliver light to peripheral nerves in naturally behaving mice during persistent locomotion (Fig. 9c) [19]. The hydrogel fibers, consisting of a crystalline polyvinyl alcohol core and a reduced graphene oxide-doped cladding, exhibited low optical losses, high stretchability, and excellent fatigue resistance against repeated deformation (Fig. 9d). These fibers enabled optogenetic activation of hindlimb muscles in transgenic mice expressing channelrhodopsin-2 and inhibition of pain hypersensitivity in mice expressing halorhodopsin over extended periods (Fig. 9e). This work demonstrates the potential of hydrogel-based materials in facilitating optical coupling with biological tissues for optogenetic applications.

The development of hydrogel-based materials with designed acoustic and optical properties, as well as their integration with other functional components, will continue to advance the field of bioelectronics. These advancements will not only enable a deeper understanding of the complex interactions between biological systems and electronic devices but also pave the way for novel diagnostic and therapeutic applications in personalized healthcare. However, integrating multiple functionalities such as electrical, acoustic, and optical coupling into a single hydrogel-based device presents significant challenges. Signal interference between different modalities is a primary concern, as electrical signals may interfere with optical readouts or acoustic wave propagation. Additionally, the power requirements for multi-modal devices increase substantially, potentially limiting their long-term operability in implantable applications. Addressing these challenges will require innovative design strategies, such as spatially separating different functional components within the hydrogel matrix or developing time-multiplexing techniques for signal acquisition and stimulation. Furthermore, the development of more efficient, low-power components and advanced energy harvesting or wireless power transfer methods will be crucial for realizing fully integrated, multi-modal hydrogel bioelectronic devices.

Targeted organ fixation through hydrogel self-morphing

While the previous sections have discussed the mechanical, electrical, acoustic, and even optical coupling achievable by hydrogels in bioelectronic applications, the fixation of hydrogels on targeted tissues or organs is a crucial consideration. Traditionally, the focus has been on hydrogel adhesion to achieve fixation [100–105]. However, adhesion-based approaches have several limitations. Firstly, they are substrate-dependent, requiring specific surface chemistry designs to achieve adhesion at particular sites. Secondly, the detachment process may cause damage to the organs or tissues. An important aspect of hydrogels that is often overlooked is their stimuli-responsive capability in bioelectronic-related applications. By designing the stimuli-responsive properties of hydrogels, active shape morphing can be achieved, which can be further exploited for targeted site fixation [56, 106, 107]. This approach circumvents the issues associated with interfacial adhesion.

Recent advancements in stimuli-responsive hydrogels have demonstrated their potential for targeted organ fixation through self-morphing. Hao et al. developed a self-shaping hydrogel-based soft electronics by creating a gradient structure in the hydrogel substrate [65]. The hydrogel, composed of a tough poly(acrylamide-co-methacrylic acid) bottom layer and a stripe-patterned polyacrylamide upper layer with varying compositions and swelling capacities, could actively deform into a cylindrical helix upon swelling in water due to the swelling mismatch between different gel regions (Fig. 10a). This self-morphing ability allowed the hydrogel device to self-roll onto a glass rod or a rubber hose with good fixation and interfacial contact, without relying on adhesion. The sensing performance of the self-rolled hydrogel device was demonstrated by monitoring the bending motions of the human finger, and the swinging of cylindrical animals (Fig. 10b).

In another work, Yi et al. designed a water-responsive supercontractile polymer film inspired by spider silk [108]. The film, composed of poly(ethylene oxide) and poly(ethylene glycol)-α-cyclodextrin inclusion complex, exhibited rapid and large contraction (over 50% of its original length within seconds) when exposed to water, transforming into a soft and stretchable hydrogel thin film (Fig. 10c and d). The supercontraction was attributed to the

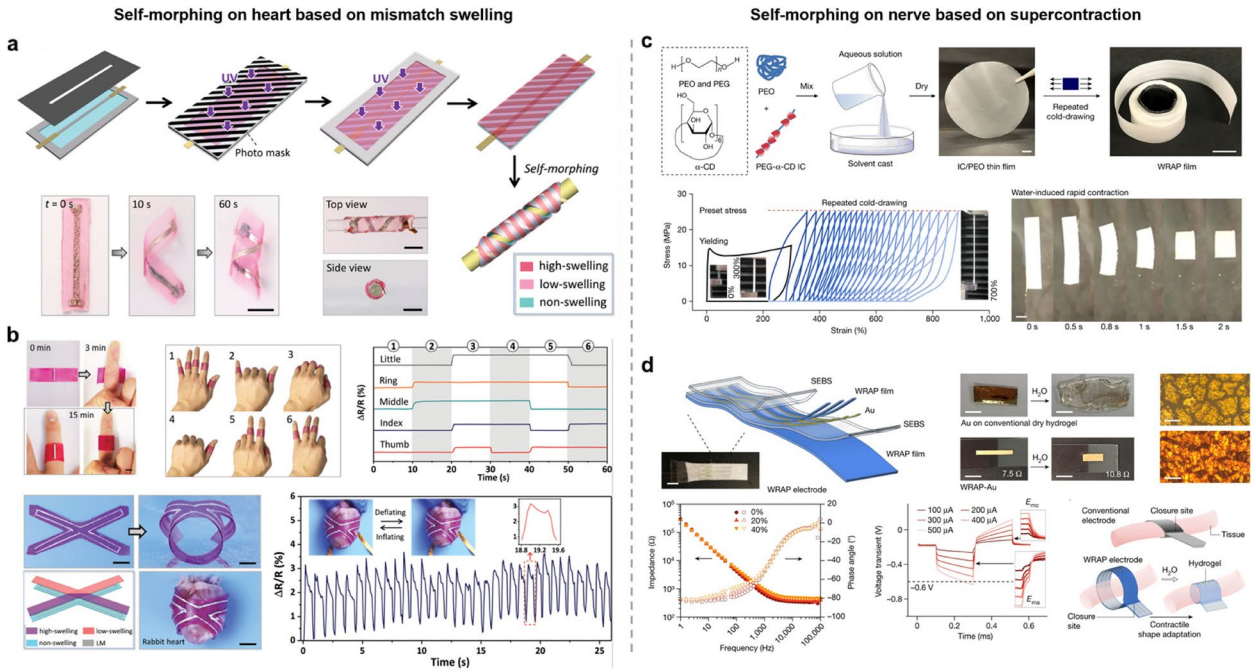


Fig. 10 Self-morphing hydrogel-based bioelectronics for targeted organ fixation. **a, b** Self-morphing on heart based on mismatch swelling: **a** Design and fabrication process of the gradient-structured hydrogel device, illustrating its self-shaping mechanism through differential swelling. Images show the morphing process and final cylindrical helix shape. **b** Demonstration of the self-morphing hydrogel device's applications, including conformable wrapping around finger joints, various cylindrical objects and its adaptability to complex organ geometries like the heart. Adapted with permission from [69]. **c, d**Self-morphing on nerve based on supercontraction: **c** Fabrication process and characterization of the water-responsive supercontractile polymer film, including its chemical composition, structural changes upon hydration, and contraction behavior. Scale bars, 1 cm (top left), 5 mm (top right); 3 mm (bottom right). **d** Application of the supercontractile film in bioelectronics, demonstrating its conformability to various structures, electrical properties, and functionality in nerve stimulation. Scale bars, 5 mm (left); 1 cm (middle); 20 μm (right). Adapted with permission from [108]

aligned microporous hierarchical structures of the films. By fabricating shape-adaptive electrode arrays using this film, the authors demonstrated conformal wrapping around nerves, muscles, and hearts of different sizes upon wetting, simplifying the implantation procedure and enabling in vivo nerve stimulation and electrophysiological signal recording without the need for adhesion-based fixation.

These studies highlight the potential of self-morphing hydrogels for targeted organ fixation in bioelectronic applications. By harnessing the stimuli-responsive properties of hydrogels, active shape morphing can be achieved, allowing conformal wrapping and fixation on tissues and organs with complex geometries. This approach offers a promising alternative to adhesion-based methods, overcoming the limitations of substrate dependence and potential tissue damage during detachment. The kinetics of the shape-morphing process in stimuli-responsive hydrogels is a critical factor for in vivo applications. The rate of shape change must be carefully controlled to allow for precise positioning without causing tissue damage. Factors influencing this process include the hydrogel's composition, crosslinking density, and the intensity of the applied stimulus. In vivo control of shape morphing could be achieved through various means, such as localized temperature changes, pH modulation, or light activation in photosensitive hydrogels. Future research should focus on developing hydrogels with multi-responsive properties that can be fine-tuned externally, allowing for real-time adjustment of the morphing process. Additionally, integrating sensing capabilities within the hydrogel to provide feedback on the morphing state could enable closed-loop control systems for precise and adaptive organ fixation. As research in stimuli-responsive hydrogels continues to advance, it is expected that more sophisticated self-morphing hydrogel devices with enhanced functionality and targeted fixation capabilities will emerge.

Wearable and implantable hydrogel bioelectronics

With the rapid development of hydrogel bioelectronics [7, 105, 106], various wearable and implantable applications have been demonstrated [109, 110] , showcasing their potential in personalized healthcare. In this section, we first focus on the recent progress of hydrogel bioelectronics in wearable applications.

Wearable hydrogel bioelectronics have been extensively studied for epidermal sensing and therapy. Zhang et al. reported a facile transfer printing method to obtain PEDOT:PSS thin films on various soft substrates, enabling the fabrication of skin-attachable organic electrochemical transistors (OECTs) [111]. The skin-attachable OECTs exhibited stable performance under mechanical deformation and were successfully applied for glucose monitoring (Fig. 11a). This work provides a versatile platform for developing flexible organic electronics based on PEDOT:PSS thin films. Huang et al. developed an injectable, self-adhesive, and antibacterial dual-conductive hydrogel for epidermal electrodes (Fig. 11b) [112]. The hydrogel was formed by the PEDOT:PSS-promoted self-polymerization of zwitterionic SBMA, resulting in a unique dual-conductive network. The in situ forming hydrogel could maintain close contact with hairy skin and establish conformal interfaces with irregular wounds. As a result, the hydrogel-based epidermal sensors could record stable and reliable surface electromyogram (sEMG) signals from hairy skin. Furthermore, the electroactive hydrogels served as electrotherapeutic dressings to accelerate diabetic wound healing. This work demonstrates the potential of in situ forming conductive hydrogels for wearable sensing and therapy.

Lim et al. reported an ultrathin, mass-permeable, and low-impedance hydrogel for a tissue-like skin-device interface (Fig. 11c) [61]. The functionalized hydrogel acted as a liquid electrolyte on the skin and formed an extremely conformal and low-impedance interface for wearable electrochemical biosensors and electrical stimulators. The porous structure and ultrathin thickness of the hydrogel facilitated the efficient transport of target molecules through the interface. Wearable devices integrated with the hydrogel interface were demonstrated for transcutaneous oxygen sensing, impedance sensing, iontophoretic drug delivery, and electrical nerve stimulation. This work highlights the importance of a tissue-like hydrogel interface for maximizing the performance of wearable bioelectronics. Li et al. developed a fully solution-processable and transparent capacitive tactile sensor using microstructured gelatin methacryloyl (GelMA) hydrogel as the core dielectric layer (Fig. 11d) [113]. A robust chemical bonding and encapsulation approach were introduced to overcome the detachment and water-evaporation issues in hydrogel-based sensors. The GelMA tactile sensor exhibited a high pressure sensitivity and a low limit of detection, as well as excellent durability and long-term stability. The sensor was successfully applied for monitoring various human physiological signals, such as pulse and vocal cord vibration. This work demonstrates the potential of GelMA hydrogels for fabricating high-performance wearable tactile sensors.

The above examples showcase the diverse applications of hydrogel bioelectronics in wearable devices, ranging from epidermal sensing and therapy to skin-device interfaces and tactile sensors. The unique properties of hydrogels, such as softness, stretchability, adhesiveness, and biocompatibility, enable the development of wearable devices with improved conformability, signal quality, and user comfort. The functionalization of hydrogels with conductive materials or biologically active molecules further expands their capabilities in wearable bioelectronics. Despite these advantages,

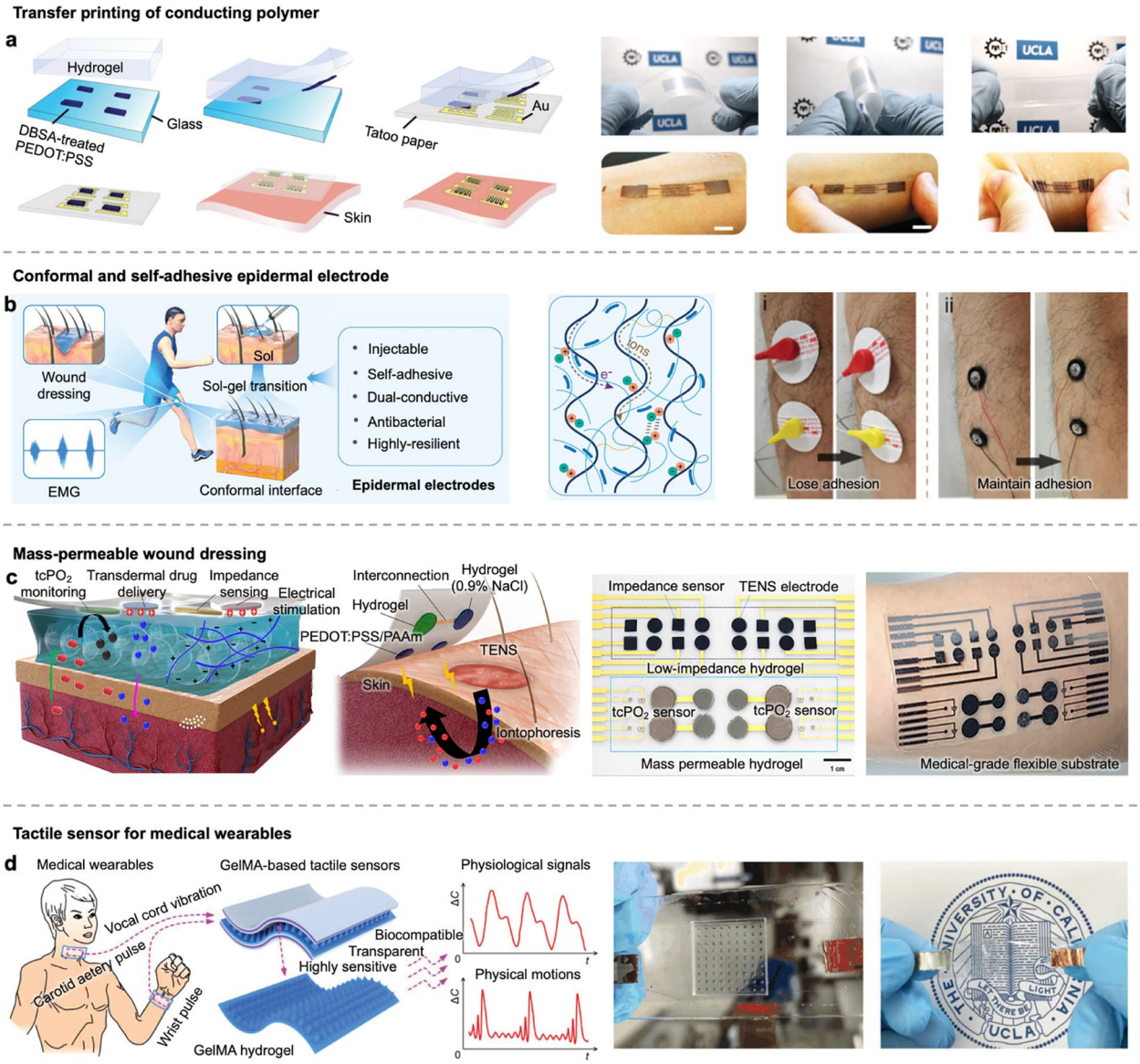


Fig. 11 Wearable hydrogel bioelectronics for personalized healthcare applications. **a** Transfer printing of conducting polymer: Schematic illustration and photographs demonstrating the process of transferring PEDOT:PSS thin films onto various substrates, including hydrogels, tattoo paper, and skin. The images show the versatility and transparency of the transferred conductive patterns. Scale bars, 1 cm. Adapted with permission from [111]. **b** Conformal and self-adhesive epidermal electrode: Conceptual diagram and images of an injectable, self-adhesive, and dual-conductive hydrogel for epidermal electrodes. The illustrations show its application for wound dressing and EMG sensing, while photographs demonstrate its adhesion properties on skin. Adapted with permission from [112]. **c** Mass-permeable wound dressing: Schematic representation of a multifunctional hydrogel-based wound dressing with integrated sensing capabilities. The images show the layered structure of the dressing, its interaction with skin, and examples of fabricated flexible electrode arrays. Adapted with permission from [61]. **d** Tactile sensor for medical wearables: Illustration and photographs of GelMA-based tactile sensors for medical wearables. The diagrams show the sensor's structure and its ability to detect physiological signals and physical motions. Adapted with permission from [113]

long-term stability and adhesion of hydrogel wearables on skin remain challenging under varying conditions. Humidity fluctuations can cause dehydration or excessive swelling, while temperature changes may alter mechanical and electrical properties. To address these issues, strategies include: (1) incorporating hygroscopic agents like glycerol to maintain hydration, (2) developing bilayer structures with a water–vapor-permeable but liquid–water-impermeable outer layer (e.g., using PDMS), and (3) utilizing dynamic crosslinking mechanisms such as reversible Diels–Alder reactions that adapt to environmental changes. These approaches aim to enhance the long-term stability and comfort of wearable hydrogel bioelectronics across diverse environmental conditions. Another critical challenge in soft

bioelectronics is motion artifact, which can significantly impact signal quality. Hydrogel-based devices offer a unique advantage in reducing motion artifacts due to their excellent adhesion and conformability to skin. The viscoelastic nature of hydrogels allows them to absorb and dissipate mechanical stresses during movement, maintaining stable skin–electrode contact. Furthermore, the ionic conductivity of many hydrogels mimics the body's natural electrical conduction, potentially reducing impedance mismatches at the skin–electrode interface. Recent studies have shown that strategically designed hydrogel interfaces can reduce motion artifacts by up to 50% compared to traditional electrodes, particularly during dynamic activities [114, 115]. Future development of hydrogel bioelectronics should focus on optimizing material properties and device structures to further minimize motion artifacts, enhancing the reliability of long-term physiological monitoring in real-world conditions.

Transitioning from wearable hydrogel bioelectronics, we now focus on implantable hydrogel devices that can interface with tissues and organs inside the body. While wearable devices offer significant advantages for non-invasive monitoring and stimulation, implantable bioelectronics enable more targeted and precise interactions with specific structures. Tringides et al. developed a fully viscoelastic electrode array that closely mimics the mechanical properties of soft biological tissues [59]. The key innovation of this work lies in the use of alginate hydrogels loaded with conductive carbon nanomaterials, which endowed the electrode array with both electrical conductivity and tissue-like viscoelasticity (Fig. 12a). This work validated the biocompatibility and functionality of the viscoelastic arrays through in vitro studies and acute in vivo experiments, demonstrating their potential for applications such as electrocorticography and peripheral nerve stimulation.

Deng et al. developed an electrical bioadhesive (e-bioadhesive) interface based on a conductive graphene nanocomposite hydrogel [116]. This e-bioadhesive interface could provide rapid, robust, and on-demand detachable adhesion to various wet dynamic tissues, facilitating the integration of bioelectronic devices (Fig. 12b). The authors demonstrated the biocompatibility, mechanical stability, and electrical functionality of the e-bioadhesive interface in both ex vivo porcine and in vivo rat models, showcasing its potential for applications such as epicardial electrophysiological

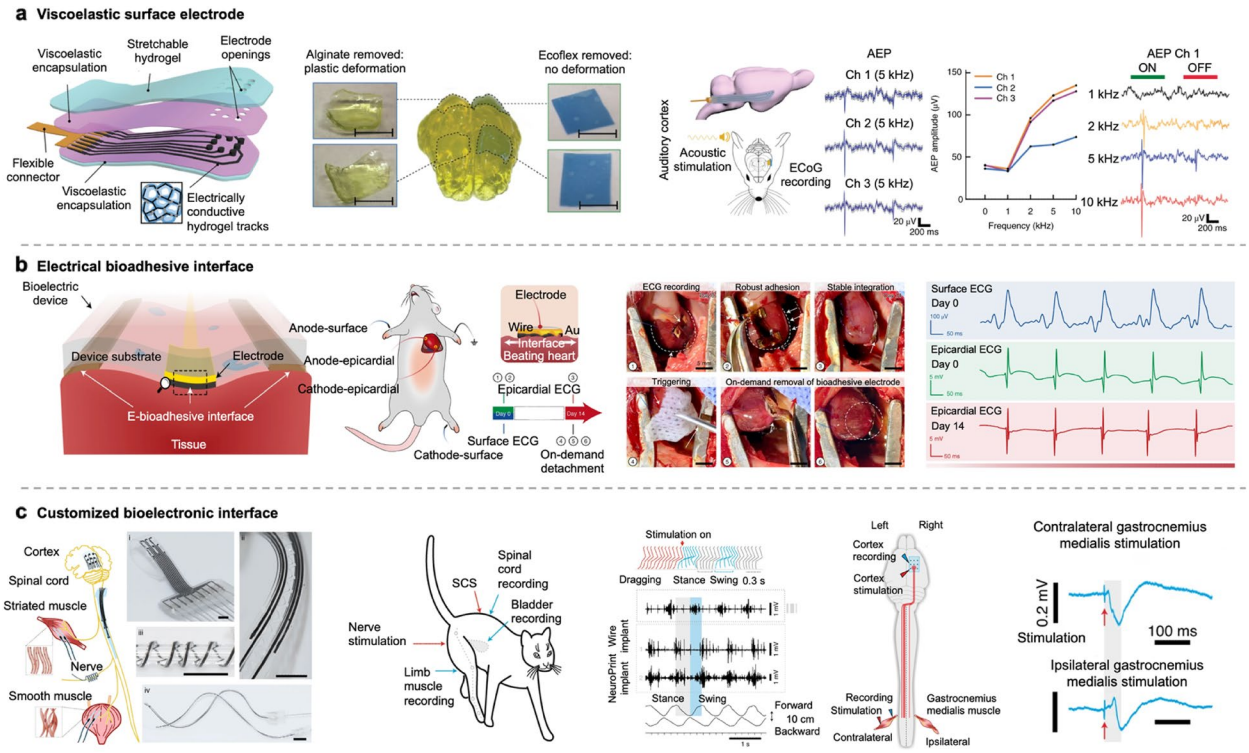


Fig. 12 Implantable hydrogel bioelectronics for personalized healthcare applications. **a** Viscoelastic electrode array: Schematic illustration and photographs of the alginate hydrogel-based electrode array loaded with conductive carbon nanomaterials.The images demonstrate its conformability to brain tissue and its application in electrocorticography.Adapted with permission from [59]. **b** Electrical bioadhesive interface: Conceptual diagram and experimental results of the conductive graphene nanocomposite hydrogel e-bioadhesive. The illustrations show its rapid adhesion to wet tissues and its use in epicardial electrophysiological mapping.Adapted with permission from [116]. **c** Customized bioelectronics interface: Illustration of the rapid prototyping process for personalized soft bioelectronic implants. The images showcase the 3D-printed electrode arrays and their application in spinal cord stimulation and peripheral nerve interfacing. Adapted with permission from [117]

mapping and sciatic nerve stimulation. In another study, Afanasenkau et al. introduced a rapid prototyping technology called "NeuroPrint" for the fabrication of personalized soft bioelectronic implants (Fig. 12c) [117]. By leveraging the capabilities of hybrid 3D printing, the authors could produce customized electrode arrays that are well-adapted to specific anatomical structures and experimental models. The NeuroPrint implants demonstrated long-term biointegration and functional stability in a rat model, with minimal neuroinflammation and preserved motor functions. Furthermore, the technology enabled multi-modal interfacing with the neuromuscular system, including spinal cord stimulation, electromyography, and nerve stimulation across different animal models. These studies highlight the growing trend of employing hydrogel-based implantable bioelectronics for various therapeutic and diagnostic applications. By focusing on the development of soft, tissue-like materials and personalized designs, researchers are pushing the boundaries of bioelectronic interfaces to achieve better biointegration, long-term stability, and enhanced functionality.

Conclusions and future perspectives

This review has examined recent advancements in hydrogel-based soft bioelectronics for personalized healthcare, focusing on three key challenges: achieving wide-range modulus coverage, balancing multiple functional properties and achieving effective organ fixation. We explored strategies for tuning hydrogel mechanical properties to match diverse tissues, from soft brain to stiff tendons, through innovative network designs. Methods for imparting conductivity to hydrogels, including ionic conductivity, conductive fillers, and conductive polymers, were analyzed for their unique advantages in bioelectronic applications. We highlighted approaches for decoupling mechanical and electrical properties in hydrogels, such as network design strategies incorporating sliding-ring structures to address the brittleness of conductive polymers, and the novel concept of all-hydrogel devices to fundamentally decouple mechanical and electrical performances. These innovations provide potential solutions to the traditional trade-offs between mechanical robustness and electrical conductivity. Beyond electrical interfacing, we discussed hydrogels' potential in acoustic and optical coupling, expanding their functionality in bioelectronics. The review introduced hydrogel self-morphing as an alternative to adhesion-based methods for targeted organ fixation, offering improved conformability and reduced tissue damage. Finally, we categorized and analyzed applications of hydrogel-based bioelectronics in wearable and implantable devices, demonstrating their versatility in personalized healthcare, from epidermal sensing and therapy to neural interfaces and bioadhesives.

The field of hydrogel-based soft bioelectronics holds immense potential for advancing personalized healthcare. However, to fully realize this potential, several key challenges and opportunities need to be addressed in future research. One critical aspect is the integration of multiple modalities, including mechanical, electrical, acoustic, and optical coupling, within a single hydrogel-based device. Advancements in soft robotics have already demonstrated the power of such multimodal integration [118–122]. For instance, Zhao et al. reported the development of a somatosensory actuator based on a stretchable conductive photothermally responsive hydrogel [118]. This innovative material integrates piezoresistive strain/pressure sensing and photo/thermal actuation functions into a single, homogeneous hydrogel. Crucially, it can simultaneously perceive its environment (exteroception), sense its own deformations in real-time (proprioception), and actuate with near-infinite degrees of freedom. By incorporating similar design principles, researchers can develop bioelectronic devices capable of closed-loop, autonomous operation. Such devices could sense physiological signals, process this information in real-time, and respond adaptively, greatly enhancing the precision and effectiveness of personalized therapies.

Another promising direction for future research lies in leveraging the power of big data and artificial intelligence (AI) to optimize the performance and adaptability of hydrogel-based bioelectronics [123, 124]. With the increasing adoption of wearable and implantable devices, vast amounts of physiological data can be collected from individual patients. By employing advanced data analytics and machine learning techniques, researchers can extract valuable insights from this data to inform the design and customization of hydrogel-based bioelectronics. For example, AI algorithms can be trained to recognize patterns and anomalies in patient-specific data, enabling the development of predictive models for early disease detection and intervention. Furthermore, AI can aid in the optimization of device parameters, such as mechanical properties, electrical conductivity, and drug release profiles, based on individual patient needs and responses. This data-driven approach will not only enhance the efficacy of personalized therapies but also accelerate the translation of hydrogel-based bioelectronics from the lab to the clinic.

Despite promising advancements, significant barriers remain in translating hydrogel technology to clinical applications. Long-term stability is a primary concern, particularly for implantable devices. For instance, current hydrogels may experience up to 50% reduction in mechanical

strength and 30% decrease in electrical conductivity over a 6-month period in physiological conditions, potentially compromising device functionality. Biosafety issues include the risk of chronic inflammation due to degradation products and potential toxicity from leaching of conductive fillers or unreacted monomers. For example, some conductive hydrogels containing silver nanoparticles have shown cytotoxicity at concentrations above 10 μg/mL. Regulatory hurdles are substantial, as the FDA currently lacks specific guidelines for hydrogel-based bioelectronics, necessitating case-by-case evaluation. Addressing these barriers requires extensive in vivo studies lasting at least 1–2 years, development of standardized accelerated aging tests, and establishment of specific biocompatibility protocols for this new class of materials. To fully harness the potential of hydrogel-based soft bioelectronics for personalized healthcare, collaborative efforts across disciplines will be essential. The development of these advanced bioelectronic systems requires the integration of expertise from materials science, bioengineering, electronics, data science, and clinical medicine. By fostering cross-disciplinary collaborations and knowledge exchange, researchers can accelerate the innovation and translation of hydrogel-based bioelectronics. Moreover, close partnerships between academia, industry, and healthcare providers will be crucial for bridging the gap between technological advancements and clinical applications, ensuring that these innovative solutions reach the patients who need them most.

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Declarations

Competing interests The authors declare no conflict of interest.

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