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MINI REVIEW

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Chemical Approaches to Emerging Advancements in Deformable Bioelectronics: Synthesis, Device Concepts, Performance, and Applications

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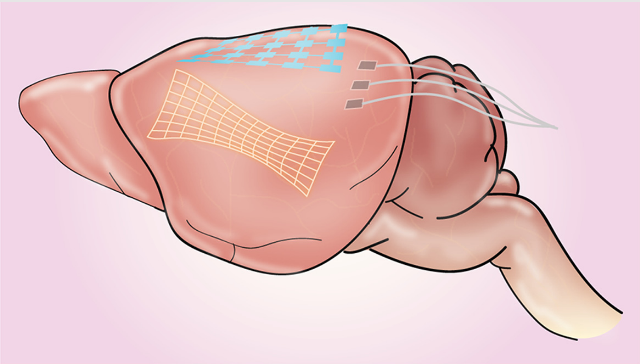
This mini review examines the current advances and future prospects of chemical approaches in deformable bioelectronics, emphasizing their transformative potential in healthcare and other sectors. The mini review outlines novel fabrication strategies that rely on chemical principles to create adaptable, comfortable, and durable bioelectronic devices that are capable of seamlessly integrating into the dynamic biological environment. The discussion also extends to the integration of innovative device concepts that enhance the outcomes in both sensing and modulation functionalities. Performance-enhancing strategies that use chemistry to refine the sensitivity and precision of these devices are also highlighted. Moreover, the mini review explores the emerging applications of chemically enhanced bioelectronic devices in healthcare, reflecting the potential of this field to revolutionize patient care and improve health monitoring. In the outlook section, this mini review investigates the promising future of transient and living bioelectronics, emphasizing the pivotal role of chemical approaches in their development. It additionally covers the potential of chemical techniques in powering bioelectronic devices using biological systems and discusses the prospective applications of chemically synthesized bioelectronic devices outside of healthcare. While the field has made substantial progress, this mini review also identifies challenges that must be addressed, thus underlining the necessity for continued research and chemical innovation in bioelectronics.



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Introduction

The emerging bioelectronics trend in healthcare aims to treat disease, heal trauma, and monitor and improve health by using innovative materials and device designs, from smart bandages to hydrogel electronics to wearable and implantable power generation. Many of these devices try to integrate electronics into the body by mimicking the surrounding organs or tissue and facilitating natural healing processes.[1-6] Thus, the devices must be flexible, gentle, and resistant to changes in the biological environment. To achieve these standards, researchers have recently innovated in flexible bioelectronics, biological modulation and sensing, and hydrogel-based bioelectronics and biointerfaces.

Flexible bioelectronics seek to adapt to an evolving biological environment to enable long-term treatment or modulation. When tissue in a patient's body changes size and shape—especially in children—the implanted bioelectronic device becomes stressed. Thus, it must either be reconfigured or replaced, inconveniencing the patient with another risky surgery.[7,8] Another challenge is that devices often mechanically differ from biological tissue. The mismatch, along with the poor quality of adhesives used, causes device interfaces to fail.[9] Many devices try to mimic the elasticity of tissue. However, they commonly comprise elastomeric thin films that lack permeability, which causes discomfort, inflames the skin over time, and inhibits the device from integrating with the body.[10] In other instances, device designs feature rubbery semiconductors, but their initial fabrication techniques are complex with little reproducibility.[11] So, the field has moved toward simpler fabrication methods—such as laser technology—and pushed for new designs and molecular engineering strategies to create self-healing and viscoplastic polymers.[12,13] These polymers, comprised of various molecular networks, allow for device deformation to resist a dynamic biological environment and adapt to the patient's changing or growing body.

A similar advancement is the application of hydrogels. Hydrogels offer a compelling alternative to traditional elastomers,[2] as they more closely mimic soft tissues' physical and chemical properties. Thus, more devices now use hydrogels to encapsulate their electronic components since hydrogels are soft, stretchable, and hold a lot of water—qualities that help them mimic soft tissues.[2,14-16] This integration of electronics with hydrogels means that hydrogels should be electrically conductive, a technology recently developed to address the lack of compressible and fatigue-resistant conductors.[17,18] Hydrogels are also often used as adhesives, which repair tissue,[19] deliver drugs,[19] and dress wounds.[3,20] The hydrogel-based adhesives help tackle the challenge of using the same material to adhere to both biological tissues and electronic devices whose softness and shape differ.[3] And hydrogels are easier to synthesize because they can be 3D printed.[2]

Deformable bioelectronics can also be useful in health monitoring devices. These devices use new polymers or materials and chemical designs to accurately mimic and sense the biological environment. Many bioelectronic devices aim to monitor serious wounds in real-time physiologically, detecting qualities including pH,[21] oxygenation,[22] impedance,[23] glucose,[24] and motion to allow more precise treatment.[1,25] Other devices monitor deep surgical sites, enabling the extra medical attention they require.[26] But they can have costly and cumbersome drawbacks that outweigh their benefits in some healthcare situations. Generally, devices that require tethering cause discomfort. And sensing devices that lack therapeutic capabilities do not help patients avoid risky medical interventions to fix the detected issues, such as biosensing bandages causing secondary damage upon detachment.[1] To address these issues, the field has been moving toward creating theranostic devices—some delivering drugs on demand,[27] others electrical stimulation when required for healing[1,28]—needing no tethering or batteries, making them more compact. And more ambitiously, other innovations seek to improve health by modulating how major body systems function, such as the digestive and central nervous systems.[29-31] These creations include artificial neurons and microbial communication devices.[30,32]

The primary challenge for bioelectronics is finding a way to make them suitable for prolonged use within the human body. Much of the in vivo testing researchers have done has used animal models over the short term.[1,3,12,26,27,29,31] And the bioelectronics' materials and designs must simultaneously be biocompatible, adaptable, comfortable, and durable. When each new device can consistently achieve all these qualities, it will bring superior patient outcomes and a new healthcare paradigm.

Emerging Synthesis or Fabrication Strategies for Deformable Bioelectronics

There has been a multitude of new synthesis and fabrication strategies for bioelectronics. Among these promising strategies are 3D printing, laser structuring, and the development of various molecular networks.

3D printing has been commonly used to print soft hydrogel electronics.[6,33] A new strategy involves the use of silver-hydrogel ink incorporated into a hydrogel supporting matrix.[2] Hui et al. created a curable hydrogel matrix utilizing an alginate-polyacrylamide (PAM) double network hydrogel, decoupling the ionic and covalent crosslinking and a stretchable, conductive, silver-hydrogel ink by mixing 5-μm-sized Ag flakes, glycerol, water-soluble polymers, and a supporting matrix gel.[2]

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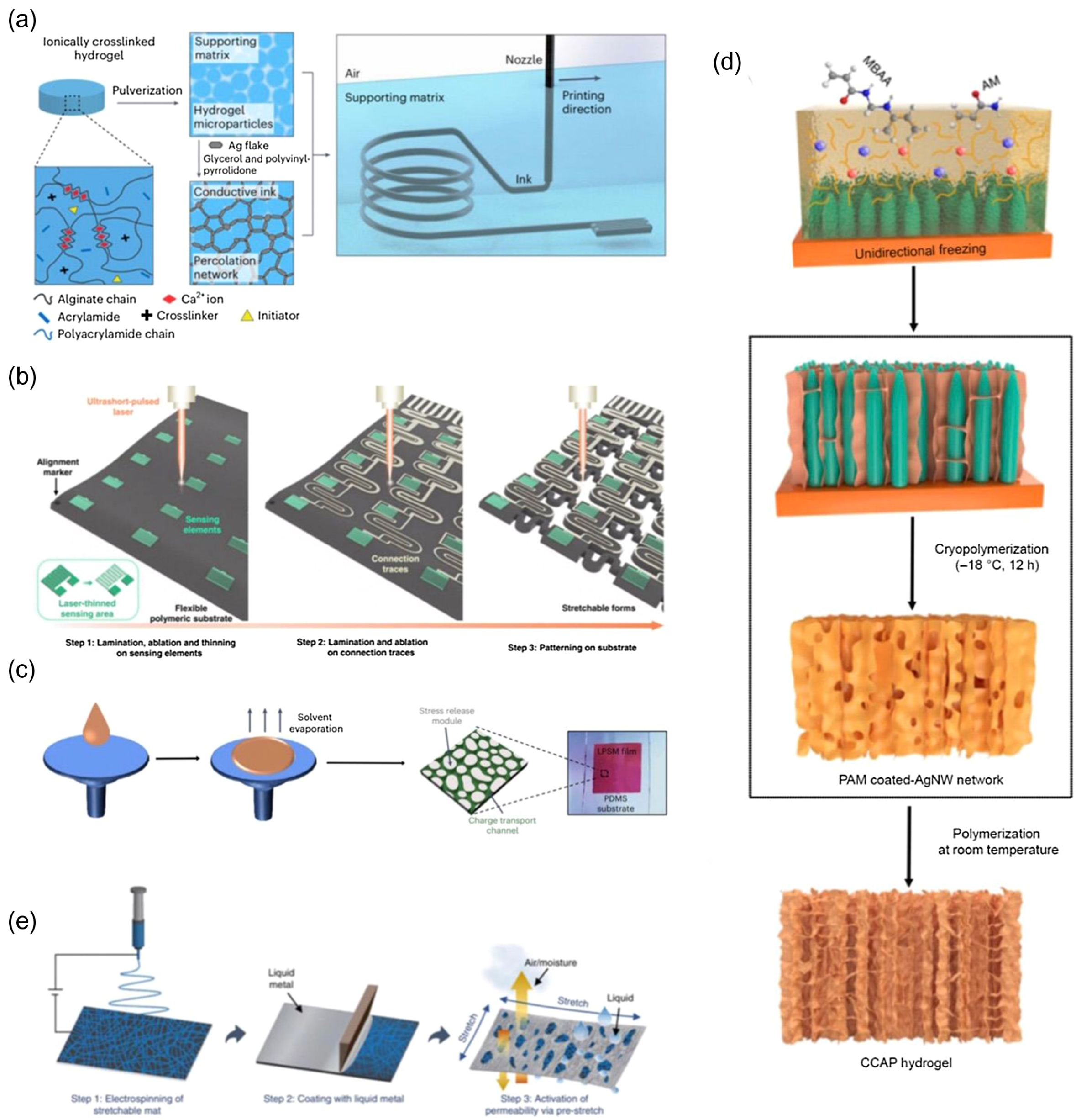

Figure 1 | *Emerging synthesis or fabrication strategies for deformable bioelectronics. (a) Schematic illustrating the conductive ink synthesis, the hydrogel supporting matrix, and the printing of the ink into the hydrogel matrix for 3D structure formation. Adapted with permission from ref 2. Copyright 2022 Springer Nature. (b) Ultrashort-pulsed laser used for patterning of film substrates. Adapted with permission from ref 34. Copyright 2022 Springer Nature. (c) Schematic showing the fabrication of the LPSM rubbery semiconductor and its three-dimensional structure. Adapted with permission from ref 11. Copyright 2022 Springer Nature. (d) Schematic illustrating the fabrication process for the CCAP hydrogel. Adapted with permission from ref 35. Copyright 2022 Springer Nature. (e) Fabrication of the liquid-metal fibre mat. Adapted with permission from ref 10. Copyright 2021 Springer Nature.*

The ink was then 3D printed into this supporting hydrogel matrix. Upon printing, the nozzle causes a shear force larger than yield stress which then causes the matrix to transform from a solid to a flowable state, allowing the nozzle to move without creating crevices in the hydrogel (Figure 1a). The fluid-state hydrogel then reverts to its solid form after the shear force vanishes, holding the silver-hydrogel ink in place without collapsing. The silver-hydrogel ink then covalently cross-links with the surrounding matrix, while the Ag flakes in the ink provide a much higher conductivity than standard ionically conductive hydrogels.

Laser technology has also been explored to aid in creating deformable bioelectronics. A picosecond ablation laser was made by Yang et al.[34] allowing for a high-speed, scanned, picosecond-pulsed laser ablation

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approach used for multilayered eco/bioresorbable materials. This approach allows for high-resolution patterning of films, thinning of films, and cutting through films and their substrates (Figure 1b). This dry laser process involves minimal laser heat generation, minimizes thermally induced degradation, minimizes damage to consistent materials, is easily controlled, and allows for the possibility of complex single- and multilayered devices.

The development of various molecular networks has also been researched to provide for bioelectronics development. Highly compressible glass-like supramolecular polymer networks (SPNs) that allow for covalent to noncovalent polymer crosslinking were developed by Huang et al. with a crosslinking design based on cucurbit[8]uril (CB[8])-mediated ternary complexation.[17] These SPNs were synthesized by photopolymerization of the 5FBVI-CB[8]-RBVI crosslinker in the presence of acrylamide. SPNs containing napthylmethyl vinylimidazolium or benzyl vinylimidazolium crosslinkers were shown to have higher loss moduli, storage moduli, and thus viscoelasticity compared to SPNs without CB[8]. Jiang et al. developed a molecular engineering strategy for high-conductivity, stretchable organic bioelectronics based on a topological supramolecular network.[12] A polyrotaxane termed TopoE was used to form a crosslinkable supramolecular additive for poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) to create a film with high conductivity, stretchability, and photopatternability to combat the decline in PEDOT:PSS performance due to the loss of noncrosslinked additives. The fabrication process optimized the chemical orthogonality and energy of elastomeric layers, developing soft and elastic electrode arrays suitable for human skin conformality for high-density surface electromyography recording. Acid-treated TopoE (Topo-ES) provides for high precision, intricate bioelectronic applications when patterned onto high-density stretchable arrays. A rubbery semiconductor film that is micromesh-structured was created by Guan et al.[11] This film was based on a lateral-phase-separation-induced micromesh (LPSM). A polymer blend solution was applied to a supporting substrate. This mixture was then spin-coated to form the film, and the solvent was evaporated to solidify it. A viscoelastic phase separation was formed, resulting in micro-sized structure formation (Figure 1c). p- and n-type stretchable semiconductors were then produced following this synthesis strategy. These strategies employ the synthesis of molecular networks, employing various interactions between molecules in the materials comprising these materials, such as crosslinking, to afford material structure.

Processes affording material structure via the self-assembly and self-organization of the molecules comprising the deformable materials for bioelectronics rather than being heavily based on interactions between different molecular components have also been explored. Wang et al.[35] established a method combining directional-freezing-induced self-assembly and two-stage in situ polymerization for AgNW–PAM (CCAP) hydrogel synthesis (Figure 1d). This freezing process was conducted at −120 °C and resulted in the creation of an anisotropic, high-tortuosity endoplasmic-reticulum-like structure and interconnected lamellar network in orthogonal directions. The self-assembly of liquid metal hanging among elastomeric fibres to form a stretchable conductor has also been explored.[10] Afforded via the coating/printing of liquid metal onto electrospun elastomeric fibre mats, this self-assembly results in a mesh-like and vertically buckled structure. Activation of permeability of this fibre mat is afforded by prestretch (Figure 1e). Such a material allows for stretchability, conductivity, and electrical stability. Aqueous droplets and hydrogel fibres have also been explored to develop novel synthetic nerves capable of parallel transmission.[30]

Emerging Deformable Bioelectronic Device Concepts

Along with the increase in synthesis or fabrication strategies for deformable bioelectronics, device concepts often incorporating these strategies have been researched. Dopamine detection and release stimulation has been mediated by using an artificial neuron composed of a dopamine electrochemical sensor, a resistive switching memristor, and a heat-induced dopamine-releasing hydrogel.[31] This artificial neuron uses this carbon-based electrochemical sensor to detect dopamine. Then, it uses the synaptic plasticity memristor to process the sensory signals. Finally, the heat-responsive hydrogel will stimulate dopamine release (Figure 2a). Recognition and memory functionalities of neurotransmitters can be implemented due to the neurotransmitter-mediated artificial synapse that includes the dopamine sensor and memristor. Another project investigated the fabrication of small synthetic nerve bundles consisting of a fascicle plus seven hydrogels serving as axons.[30] Requiring signal propagation, the researchers used lipid bilayers connecting hydrogel fibres and nanoliter aqueous droplets to create the neurons. In this neuron, ion-conducting protein pores mediate while light-driven proton pumps enable signal transmission. This synthetic nerve bundle allows for parallel transmission along three of the seven axons. However, a limitation of this technology is that when the ions used for the artificial nerve's illumination run out, the nerve's life span will also be depleted.

Artificial neurons are one of the many devices that have recently been researched.[36–38] In addition to them, other devices that enable modulation and bioelectronic communication have also been explored. Using a redox signal transduction modality, Terrell et al.[32] developed a bioelectronic communication system using a naturally

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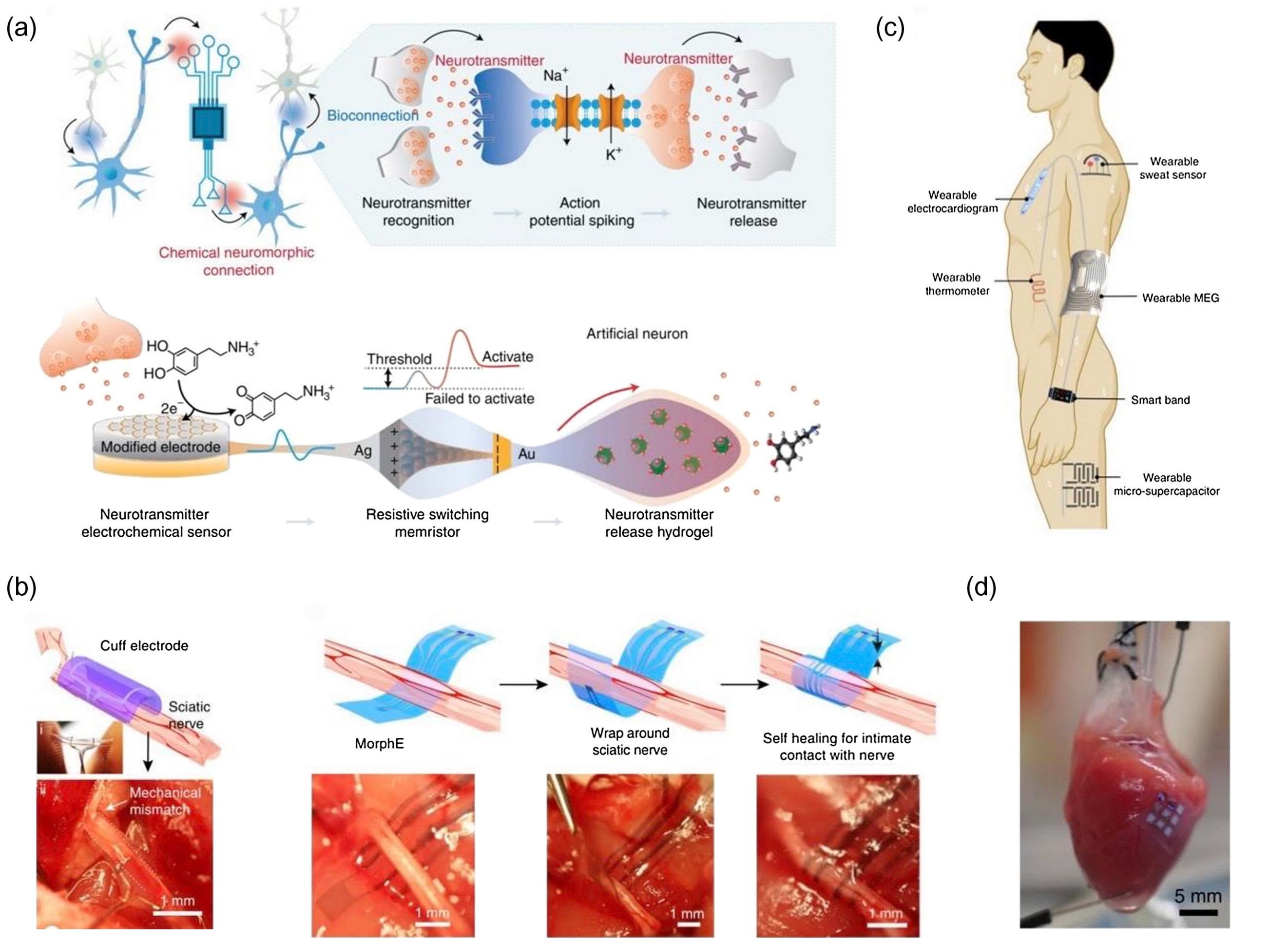

Figure 2 | *Emerging deformable bioelectronic device concepts. (a) Schematic of an artificial neuron mediated by neurotransmitters. Adapted with permission from ref 31. Copyright 2022 Springer Nature. (b) Cuff electrode and MorphE implantation and conformation around the sciatic nerve. Adapted with permission from ref 7. Copyright 2020 Springer Nature. (c) Schematic of the soft magnetoelastic generator application as a small wearable power generation source. Adapted with permission from ref 39. Copyright 2021 Springer Nature. (d) The nanoporous/nonporous, soft-hard heterojunction in p-type silicon membrane applied to the heart. Adapted with permission from ref 41. Copyright 2022 Springer Nature.*

communicating three-member microbial network that controls biological function. The biological local area network, comprised of the flow of information between the electronic system and engineering microbial cells, is electrochemically plugged into an external electronic system, allowing for bioelectronic control. Surface-assembled electrogenetic cells were synthesized to allow for direct assembly onto electrodes, allowing for signal transfer localization. Programmed electrode-generated redox molecules activate gene expression in electrode-attached bacterial cells, which biologically interpret and transmit electronic signals. These electrogenetic cues are propagated via the redirection of native cell-to-cell communication, enabling the expression and secretion of peptides and direct electronic feedback. Such developments are useful for bioelectronic control of such microbial systems using the biological local area network.

However, such bioelectronics often need help incorporating into their target tissues due to limits in adapting the devices to the tissue. As a result, researchers have developed multilayered morphing electronics to improve upon the fixed dimensions of these electronics. The multilayer morphing electronics are comprised of viscoplastic electrodes and a strain sensor, which reduce the electronic-growing tissue interfacial stress commonly hindering these electronics' implementation.[7] The viscoplastic conductive polymer and an insulating and self-healable viscoplastic polymer compromising these morphing electronics allow for long-term, irreversible deformation, helping to give these morphing electronics growth-adaptive and self-healing properties (Figure 2b).

Deformability of devices onto target tissue proves necessary, but devices that employ organ sensing also often require magnetic properties. To address this, many

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different electromagnetic composites have also been explored for applications to biomedical devices. A soft magnetoelastic composite of liquid-metal coils patterned on polydimethylsiloxane acting as a magnetic induction layer was developed for skin adhesives, stretchable bioelectronics, and water-resistant magnetic generators.[39] The researchers saw a sizeable magnetoelastic effect in a micromagnetic and porous silicon rubber matrix soft system. Biomechanical-to-magnetic energy conversion is improved, the mechanical modulus is reduced, and mechanical deformation is favored by this porous structure. From this, a soft magnetoelastic generator was produced, allowing for shaping and twisting to conform to human skin. Such a device can be used for many biological monitoring systems, such as thermometers and sweat sensors that lie on the skin of the human body (Figure 2c). Polymer-ceramic piezoelectric composites have been inhibited by their low crystallinity and weak spontaneous polarization. Su et al.[40] used Ti3C2Tx MXene nanosheets to anchor the local dipole moment and β phase content of piezoelectric polymer composites to address these hindrances. Ti3C2Tx MXene templating was used to create this high-performance piezoelectric composite. The MXene-enabled piezoelectric composite has been shown to be effective in applications for force sensing and gait monitoring.

Device concepts can also involve other properties in addition to magnetoelastic effects. One such property is photoelectrochemical. A nanoporous/nonporous, soft-hard heterojunction in p-type silicon has been synthesized for eliciting a photoelectrochemical response from semiconductor surfaces for biomedical applications.[41] Free-metal stain etching with hydrofluoric acid and nitric acid was used to create this nanostructure directly in p-type silicon. This porosity-based heterojunction can be used for optoelectronic modulation of tissues to convert low optical power into bioelectrical stimulation. It was demonstrated that this device (Figure 2d) can elicit a slow atrioventricular node rhythm ex vivo and can be used to modulate sciatic nerves in vivo.

Emerging Strategies to Improve the Performance of Deformable Bioelectronics

Deformable bioelectronics have shown great potential for increased integration into tissue, but challenges still lie in the way of increasing the efficacy of such devices. Developing hydrogels, adhesives, and hydrogel adhesives for incorporation as part of deformable bioelectronic development has been beneficial in increasing their efficacy through improvements in conductivity, confocal contact, and adhesion.

Hydrogels are of great interest in deformable bioelectronics due to their potential for deformability and, thus, conformability with biological tissue, given control of their compositions and synthesis. Different hydrogel compositions affect their properties and, thus, their biological use and compatibility. Improvements in the conductivity of these hydrogels through novel synthesis strategies, specifically, have been sought after in research.[42-44] A soft and deformable hydrogel composite composed of conductive a silver–PAM–alginate composite allows for high electrical conductivity and delivery of direct current (Figure 3a) has been produced by Ohm et al.[45] This hydrogel was synthesized using PAM-alginate hydrogel mixed with low concentrations of silver flakes. This hydrogel composite was then partially dehydrated to allow for the development of electrically conductive pathways. This synthesis allows for electrically conductive networks that are robust to mechanical deformations while also allowing for a hydrogel with low Young's modulus and high stretchability and electrical stability, enabling its beneficial incorporation into soft bioelectronics.

Strategies involving hydrogels and adhesive technologies have been researched to improve deformable bioelectronic performance. Of these strategies, improving the viscoelastic properties of hydrogels has been important in achieving conformal biointerfaces. One of the strategies to achieve this involves electrode arrays. Such bioelectronic arrays involve metals that can be used to invoke electrical properties. A surface microelectrode array using viscoelastic materials rather than encapsulation and conductive components has been developed (Figure 3b).[46] An alginate matrix enhanced with carbon nanomaterials hydrogel-based conductor was synthesized. This hydrogel was then used as an outer layer of the electrode arrays to allow enhanced conformation of the electrode array to brain tissue. A viscoelastic encapsulation layer 15 μm wide of physically entangled viscoelastic material covalently attached to 100 μm alginate-based tough gel and an insulation layer based on polydimethylsiloxane (PDMS) physically entangled with amine-terminated PDMS to aid in self-healing were both created for this array. The resulting array was both viscoelastic and conformable to brain and cardiac tissues.

The potential of hydrogels and polymers for adhesion to further incorporate themselves into their target biological tissue has also been researched.[47-49] Accordingly, improvements in hydrogel adhesion have been explored. Xu et al.[50] created a hydrogel adhesive self-assembly strategy for biomimetic electroconductive liquid metal hydrogels. Such a hydrogel contains a highly complex reversible polymer network.[50] This self-assembled hydrogel was synthesized by mixing polysaccharides, conductive biopolymers, and liquid metal nanodroplets in convergent synthesis, affording such a polymer network. This network provides self-healing and shear-thinning properties and enhanced electroconductivity, injectability, and adhesiveness. A self-adhesive conductive polymer composite for

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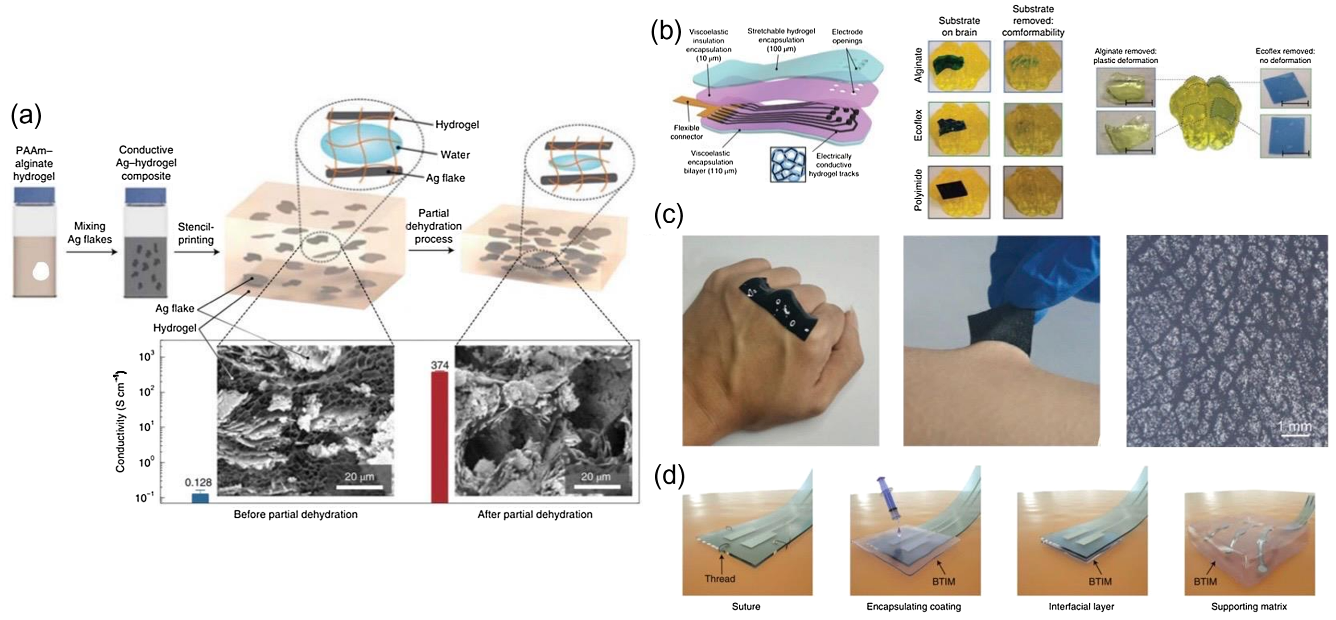

Figure 3 | *Emerging strategies to improve the performance of deformable bioelectronics. (a) Synthesis and composition of the AG-flake-polyacrylamide-alginate conductive hydrogel composite with conductivity micrographs before and after controlled partial dehydration processes. Adapted with permission from ref 45. Copyright 2021 Springer Nature. (b) Illustration of viscoelastic surface electrode array device and the conformability of the alginate hydrogel to complex target tissue. Adapted with permission from ref 46. Copyright 2021 Springer Nature. (c) Self-adhesive conductive polymer (SACP) film conformability to finger and arm skin with an illustration of skin texture patterned on the peeled-off film. Adapted with permission from ref 9. Copyright 2022 Springer Nature. (d) Schematic of the suturing process using bioresorbable adhesives. Adapted with permission from ref 3. Copyright 2021 Springer Nature.*

soft electronics has been developed (Figure 3c).[9] This polymer composite is synthesized by doping PEDOT:PSS composites with a biocompatible supramolecular solvent which then mixes these PEDOT:PSS composites and biocompatible supramolecular solvent with polyvinyl alcohol covalently crosslinked by glutaraldehyde and the conductive polymer (PEDOT:PSS). This mixture is then dried to form the self-adhesive conductive polymer (SACP). This polymer exhibits low residual strain, low modulus, high conductivity, high stretchability, and strong interface adhesion strength. This polymer's films have great potential for use in bioelectronics requiring conductive interfaces with the adhesiveness of human skin.

Because strategies to improve deformable bioelectronic materials' adhesive properties are important, improvements in nonhydrogel-based adhesives have also been looked into. Yang et al.[3] created a bioelectronic–tissue interface material that consists of mechanically compliant, electrically conductive, and optically transparent encapsulating coatings with strong adhesive qualities. This material utilizes polyethylene glycol-lactide acid diacrylate combined with sodium alginate to create a material that initially flows viscously and later conforms to surfaces (Figure 3d). The bioelectronic–tissue interface material can be used as interfacial layers that support matrices or encapsulate coatings.

Emerging Applications in Deformable Bioelectronics

Due to the increasing availability of deformable electronics that can conform to target tissue due to advances in conformational adaptation strategies, further applications for deformable bioelectronics are needed. Many of these applications, of course, involve electrical sensing and regulation.[7,51,52] With the multitude of applications, comes a multitude of organ systems and diseases that these deformable bioelectronics can target.

One of these target systems is the eye. A theranostic contact lens (Figure 4a) has been developed by Yang et al.[27] This contact lens detects intraocular pressure with a capacitive sensing circuit that allows for the ultrasensitive detection of fluctuations in intraocular pressure by a wireless pressure-sensing modulus. The drug delivery modulus then triggers drug delivery in the aqueous chamber. This technology, of course, is wireless, noninvasive, and cost-effective.

In addition to applications in the eye, bioelectronic devices are important for their wound healing and skin monitoring capabilities.[25,53–55] A wireless, closed-loop, smart bandage has been created for on-demand adhesion and attachment (Figure 4b).[1] This device consists of

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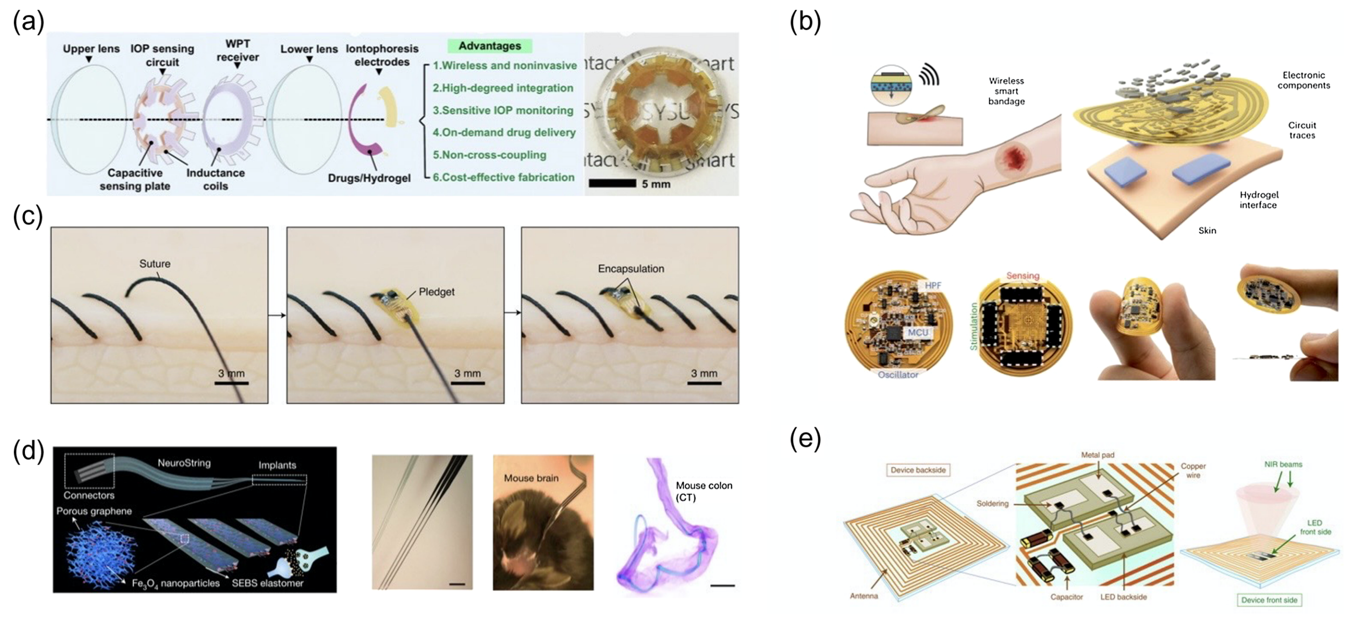

Figure 4 | *Emerging applications in deformable bioelectronics. (a) Schematic of the theranostic contact lens structure. Adapted with permission from ref 27. Copyright 2022 Springer Nature. (b) Smart bandage design schematic. Adapted with permission from ref 1. Copyright 2022 Springer Nature. (c) Schematic of multifilament surgical sutures with electronic pledget surgical implantation. Adapted with permission from ref 26. Copyright 2021 Springer Nature. (d) Schematic design of NeuroString and implementation into a mouse brain and colon. Adapted with permission from ref 29. Copyright 2022 Springer Nature. (e) Schematic showing the design of the subcutaneously implanted, wirelessly powered light-emitting device. Adapted with permission from ref 57. Copyright 2022 Springer Nature.*

skin-interfacing hydrogel electrodes that monitor the progression of wound healing. Specifically, soft hydrogels with on-demand adhesion, high toughness, and low contact impedance are beneficial for creating such smart bandages. A battery-free flexible printed circuit board is added to the conductive and adhesive hydrogel interface to allow for wound treatment and monitoring. Wireless, bioelectronic sutures have all been created for applications to surgical wounds.[26] These are multifilament surgical sutures consisting of a conductive polymer of PEDOT:PSS with pledgets with capacitive sensors incorporated in them (Figure 4c). These sensors operate using radio-frequency identification and can thus be used to view the surgical site's physiochemical states. These sutures have properties and efficacies comparable to that of standard medical sutures and can now monitor deep wound healing.

Gut and nervous system applications have also been targets of interest for deformable bioelectronic research. NeuroString (Figure 4d) is a soft and stretchable graphene-based biosensing neural interface created by Li et al.[29] that allows for monoamine sensing in the brain and the gut. Graphene was used as NeuroString's electrode with embedded laser-induced graphene nanofibre networks to afford the material's softness, stretchability, and electrochemical properties. NeuroString can also be applied to sense monoamine neurotransmitters in other soft organs. With similar goals, another research group created an ingestible bioelectronic device from environmentally resilient biosensor bacteria, reinforcing that the field can use biological systems for sensing and electronics to process and communicate information.[56] The bacteria, with their complex genetic circuits, can detect analytes that indicate human health and harmonize with the human gut with their probiotic qualities. The researchers link these biosensing bacteria to readout electronics by using light: the bacteria emit light when detecting biomarkers, the electronics have photodetectors transmitting electrical signals to a detection circuit, and the signals are then wirelessly transmitted to an external radio. As researchers improve both microelectronics and the ability to modify bacteria, this type of system will feature higher signal-to-noise ratios, better sensitivity to analytes, and expanded applications in different body systems.

Apart from organ-specific applications of deformable bioelectronics, advances in disease-specific applications have also been pursued. In particular, cancer treatment applications have been researched. One type of such disease treatment is photothermal therapy. The use of gold nanostars has been shown to aid in the treatment of brain tumors.[57] The researchers made a subcutaneously implanted, wirelessly powered, light-emitting device

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(Figure 4e) tuned to generate tissue-penetrating light to cross the tissue barrier and photothermally activate nanoparticles in select brain regions. They also used their gold nanostars, tuning them to this wireless transfer rate. These nanostars are then administered intratumorally and are activated by the light-emitting device to treat the brain tumor.

Outlook

The bioelectronics field has developed in various ways, working to ultimately improve patient outcomes. New synthesis strategies enable superior materials and cheaper mass production of bioelectronics. They also allow devices to seamlessly integrate into the body, devices such as artificial neurons and piezoelectric generators that turn body motion into electricity.

Still, the bioelectronics field has several challenges to overcome regarding chemical approaches. First, since healthcare devices often need to be in a biological environment for decades, if not a lifetime, the stability of their materials still needs to be improved. Indeed, the field is also limited by the difficulty and dearth of long-term studies on patients using bioelectronics since the technology is novel, and it can be challenging to perfectly predict the viability of newly designed materials for their long-term use, especially if they may be cytotoxic. Second, although some progress has been made in improving the adhesiveness of bioelectronic materials, strong and durable adhesion in the wide range of situations that biological tissues present is still a challenge. Third, specifically within the field of hydrogel bioelectronics, creating conductive hydrogels precisely while scaling existing methods remains difficult. Finally, as bioelectronics become increasingly common, the field must heed the environmental impact of creating such devices: the onus to develop devices with more sustainable and biodegradable materials complicates the need for resilient devices for long-term use in the body.

Despite these challenges, the emerging applications of flexible bioelectronics reflect a shifting paradigm in healthcare. First, flexible bioelectronics do not just enable specific bioelectronics' better integration into the body; they also suggest that bioelectronic devices can be made customizable to patients' individual needs, including for young, growing patients. With greater flexibility and deformability, the ideal is for devices to interact more naturally with biological tissues. Next, bioelectronics for sensing biochemical changes could revolutionize healthcare. Collecting real-time patient data can enable early detection, improve disease management by allowing immediate intervention during acute situations, and encourage patients to adhere to treatment plans. Moreover, sensing bioelectronics will ideally reduce the need for invasive procedures for healthcare, even mild ones such as blood tests. As the sensing capabilities improve, a wider range of smart devices will emerge that modulate their therapeutic output based on real-time biochemical data. Finally, hydrogel-based bioelectronics will allow the field to create new devices that interact with vital muscular organs such as the heart and digestive system without the devices losing their structural integrity. Hydrogels' easy fabrication with 3D printing will open new possibilities for bioelectronic devices and designs.

And beyond these applications are transient bioelectronics, living bioelectronics, and bioelectronics for nonhealthcare applications. A reason for transient bioelectronics is that creating devices for seamless use in the central and peripheral nervous systems is complex and delicate. Transient devices can monitor the body during the treatment period. One such innovation is bioresorbable silicon electrodes, which can record in vivo electrophysiological signals from the brain's surface and near the skull and scalp.[58] Since the device is bioresorbable, it is designed for temporary monitoring following procedures to install other in vivo devices, such as pacemakers. Furthermore, a bioelectronic device can not only monitor for mental illness—such as depression—after neurosurgery but during surgery to guide surgeons operating on complex nerve structures. These applications will speed up otherwise cumbersome procedures, make them less risky, and improve patient outcomes. A second type of transient bioelectronics explores the gut microbiome. An example is ingestible electronic capsules for biosensing. A research group reported a device that could sense oxygen, hydrogen, and carbon dioxide in the gut, aiming to create gas profiles of human subjects in the trial.[59] Since gas profiles reflect the gut microbiome's fermentative activity, changing gas profiles could diagnose disease. The device, a capsule, is made from a polyethylene shell encapsulating electronics, which includes a transmission system, silver-oxide batteries, a microcontroller, a temperature gauge, and gas sensors operational in both aerobic and anaerobic conditions. This technology opens possibilities for research on how food affects the microbiome and how gas profiles reflect health.

To improve the ability to create microbial biosensors, one research group created a bottom-up process to assemble living materials for endogenously constructing synthetic cells based on prokaryotes.[60] A strong example of living bioelectronics, these synthetic cells are membrane-bound, molecularly crowded, and sophisticated in composition, structure, and morphology. This implies creating artificial organelles resembling lysosomes, peroxisomes, and storage granules and reorganizing these organelles within a membrane. This versatile model provides guidance for creating symbiosis within synthetic-living cell hybrids, possibly inspiring more sophisticated systems to improve synthetic biology as a tool for diagnosis and therapy.

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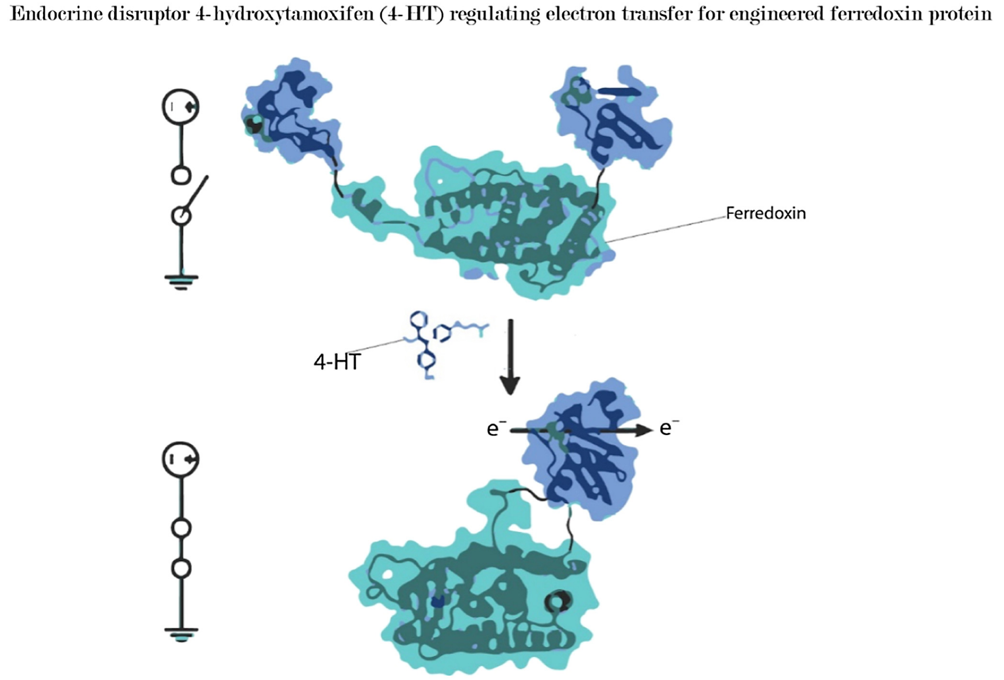

Figure 5 | *Schematic illustrating a lab-engineered electron transport chain used to program bacteria by generating an electrical current in specific environments. Adapted with permission from ref 62. Copyright 2022 Springer Nature.*

Another way researchers have used living organisms is to create potential power sources for bioelectronics.[61] So, one research group created an electrical-eel-inspired power source made from hydrogels with selective membranes. The artificial electrical organ uses thousands of stacked hydrogel compartments to establish ion gradients, enabling the device to generate electricity of up to 100 V when mechanically stressed. After the ionic gradients become compromised when they create electricity, the researchers applied a current to the terminal electrodes of the organ to recharge it. Soon, by improving the organ and recharging mechanism, the organ will be able to power implants and wearable bioelectronics that normally would be infeasible because of power demands.

Beyond healthcare, researchers have created living biosensors using *E. coli* to detect environmental contaminants in real time.[62] They programmed the bacteria using an electron transport chain—engineering the protein ferredoxin—to generate an electrical current within a few minutes when the bacteria detected specific chemicals, such as thiosulfate, that cause microbial blooms and endocrine disruptors in urban waterways (Figure 5). This research shows that electron transport chains can be reconfigured to transmit data and energy from biology to electronics, enabling continuous environmental sensing. Otherwise, continuous sensing through conventional methods, like biosensors using nucleic acids to recognize molecules, tends to fail in dynamic environments like urban waterways.

Bioelectronics can also be used to solve other challenging problems. Researchers have created bioelectronic plant wearables to control and monitor their physiology and microclimate; others have implanted enzymatic biofuel cells into plants to generate electricity from the redox reaction involving glucose and oxygen.[63] Scientists have also been exploring bioelectronics in food science, creating electronic tongues for applications from standardizing taste to exploring taste responses at the molecular level to detecting bitter compounds for the pharmaceutical industry.[64] Thus, much of bioelectronics tries to learn from nature to create new technologies that can improve lives and solve big societal problems (Table 1).

Author Contributions

J. A.-H. and A. M. wrote the manuscript. B.T. supervised the work and edited the manuscript.

Declaration of Interests

The authors declare no conflict of interest.

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Table 1 | *Table Summarizing Various Key Technologies, Their Defining Characteristics, Innovations, and Potential Areas for Improvement*

Technology Type	Technology	Defining Characteristics	Innovations	Potential Areas for Improvement
Hydrogel synthesis strategy	Silver-hydrogel ink for 3D printing into a hydrogel supporting matrix.[2]	• Covalent cross-linkage of silver-hydrogel ink with the surrounding hydrogel supporting matrix.	• The nozzle can 3D print into the hydrogel supporting matrix without creating crevices. • The silver-hydrogel ink is held in place without collapsing. • Higher conductivity than normal ionically conductive hydrogels.	• N/A
Hydrogel	Soft and deformable hydrogel composite for incorporation into soft biolelectronics.[45]	• Composed of conductive silver–polyacrylamide–alginate.	• High electrical conductivity and delivery of direct current. • Robust to mechanical deformations. • Low Young's modulus. • High stretchability and electrical stability.	• N/A
Hydrogel	Surface microelectrode array.[46]	• Uses viscoelastic materials rather than encapsulation and conductive components.	• Is viscoelastic and more conformable to brain and cardiac tissues.	• The electrodes' track width limits the arrays. • Complex geometries could be recorded by implanting the arrays into larger brains. However, this is not currently possible without the tissue attaining plastic damage.
Hydrogel-based device	Artificial neuron.[31]	• Composed of a dopamine electrochemical sensor, a resistive switching memristor, and a heat-induced dopamine-releasing hydrogel.	• Allows for dopamine detection and release stimulation.	• System-level performance needs to be explored, such as systematic encapsulation, response speed, and energy consumption for the device's practical applications.

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Table 1 | *(Continued)*

Technology Type	Technology	Defining Characteristics	Innovations	Potential Areas for Improvement
Hydrogel-based device	Synthetic nerve.[30]	• Consists of a fascicle plus seven hydrogels serving as axons.	• Allows for parallel transmission along three of the seven axons.	• When the ions used for the artificial nerve's illumination run out, the nerve's life span will also deplete. • Need to investigate the lifespan of the synthetic nerve. • Device robustness and rupture prevention when transferred to aqueous environments could be improved via the use emulsion stabilizers or block copolymers. • Adding lipids to the elastomeric sheath can allow oil removal, which may allow the transfer of droplet-based networks from oil to water. • Future research could involve adapting the synthetic nerves to function in aqueous environments.
Device concept	Multilayered morphing electronics.[7]	Comprised of viscoplastic electrodes and a strain sensor.	• Allows for the reduction of the electronic-growing tissue interfacial stress commonly hindering these electronics' implementation. • Has growth-adaptive and self-healing properties. • Allows long-term, irreversible deformation.	• More strategies to prevent plasticizer diffusion from the viscoplastic conductor and more in vivo investigation are needed to allow for prolonged stable operation of a novel viscoplastic system in human body tissue.
Adhesive	Hydrogel adhesive self-assembly strategy for biomimetic electroconductive liquid metal hydrogels.[50]	• Contains a highly complex reversible polymer network.	• Provides self-healing, shear-thinning properties, and enhanced electroconductivity, injectability, and adhesiveness.	• More research is needed to apply adhesives outside cell culture and tissue engineering.

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Table 1 | *(Continued)*

Technology Type	Technology	Defining Characteristics	Innovations	Potential Areas for Improvement
Adhesive	Self-adhesive conductive polymer composite for soft electronics.[9]	• Involves covalent cross-linkage involving PEDOT:PSS.	• The polymer exhibits low residual strain, low modulus, high conductivity, high stretchability, and strong interface adhesion strength. • The polymer's films have great potential for use in bioelectronics requiring conductive interfaces with the ability of human skin adhesion.	• N/A
Adhesive	Bioelectronic–tissue interface material.[3]	• Consists of mechanically compliant, electrically conductive, and optically transparent encapsulating coatings with strong adhesive qualities.	• Can be used as interfacial layers, supporting matrices, or encapsulating coatings.	• More interfacial chemistry research may extend the lifetime of the material through more robust, stable bonding.
Molecular network	Highly compressible glass-like supramolecular polymer networks (SPNs).[17]	• Allow for covalent to non-covalent polymer crosslinking.	• Has higher loss moduli, storage moduli, and viscoelasticity.	• N/A
Molecular network	Molecular engineering strategy based on a topological supramolecular network.[12]	• The film is created by use of TopoE to form a cross-linkable supramolecular additive for (PEDOT:PSS).	• Allows for highly stretchable organic bioelectronics. • Film is highly conductive. • Has high photopatternability. • Combats decline in PEDOT:PSS performance due to the loss of non-crosslinked additives.	• N/A

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