Perspective

Perspectives on tissue-like bioelectronics for neural modulation

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SUMMARY

Advances in bioelectronic implants have been offering valuable chances to interface and modulate neural systems. Potential mismatches between bioelectronics and targeted neural tissues require devices to exhibit "tissue-like" properties for better implant-bio integration. In particular, mechanical mismatches pose a significant challenge. In the past years, efforts were made in both materials synthesis and device design to achieve bioelectronics mechanically and biochemically mimicking biological tissues. In this perspective, we mainly summarized recent progress of developing "tissue-like" bioelectronics and categorized them into different strategies. We also discussed how these "tissue-like" bioelectronics were utilized for modulating *in vivo* nervous systems and neural organoids. We concluded the perspective by proposing further directions including personalized bioelectronics, novel materials design and the involvement of artificial intelligence and robotic techniques.

INTRODUCTION

The bioelectric modulation of neural activity has evolved rapidly in recent years. Among these are electrode-based implantable neural electrodes that can be used to record and regulate neural activity down to a single neuron level,[1,2] multi-electrode arrays for brain organoids electrophysiological measurement of high density in 2D and 3D, and peripheral nerve interfaces (PNIs) with both excitation and inhibition modes.[3–7] Such devices are often incorporated within a greater "tissue-like" material that mimics the mechanical properties of nervous tissue to ensure better integration into the nervous system. Several materials can contribute to these "tissue-like" properties, including ultrathin metal or semiconductor layers, hydrogels, conductive polymers, hydrogels incorporated with nanomaterials, and elastomeric nanocomposites.[8]

The efficacy of such bioelectronic devices as 'tissue-like' materials is, however, subject to many challenges. In many electrode-bound devices, the materials are primarily metals (which have a larger Young's modulus and are more rigid and flat than natural soft neural tissue) and other inorganic materials such as silicon. Material differences between these devices and their target tissues create a mechanical mismatch.[9–13]

The mechanical mismatch is characterized by possible mismatches between stiffness (Young's moduli), tensile strength, toughness, viscoelasticity, adhesion properties, and structural parameters such as geometry. When electrode-containing devices are mechanically mismatched to target neural tissues, it would produce damage and inflammation to the neural tissues, leading to degradation of endogenous electrophysiological signals during chronic signal recordings.[3,8–10,14] In addition, scarring caused by inflammation reduces the effectiveness of signal transmission. In addition, it is not uncommon for surgical procedures such as placing deep brain stimulators to damage nerves, damage blood vessels, provide residue pressure after implantation, and trigger an acute inflammatory response. The intrinsic (i.e., physical characteristics of the materials or devices) and extrinsic (i.e., surgical procedures) factors have posed several significant challenges in traditional implantable bioelectronic devices.[15,16]

Recent research has demonstrated the possibility of improving such mismatches or damages by creating better "tissue-like" materials for neural modulation. First, many strategies have been developed to enable stretchability and deformability. As an example, bioelectronic systems can be made more flexible by incorporating soft, stretchy, or porous materials, such as polymers and hydrogels, to hold metal electrodes or inorganic semiconductors in place. Conducting hydrogel electrodes also reduces tissue interfacial resistance, enhancing the bioelectronic signal transduction. Because hydrogels are soft, having Young's moduli

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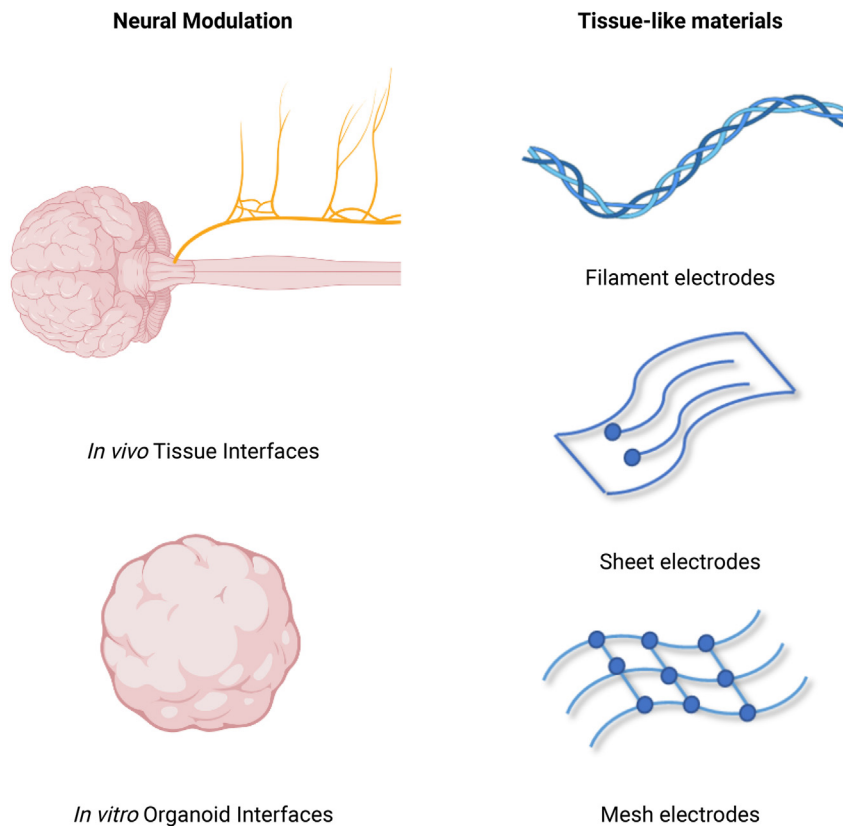[2]Department of Chemistry, University of Chicago, Chicago, IL 60637, USA

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Neural Modulation

In vivo Tissue Interfaces

In vitro Organoid Interfaces

Tissue-like materials

Filament electrodes

Sheet electrodes

Mesh electrodes

Figure 1. Tissue-like material geometries for neural modulation

similar to those of neural tissue, and have water preservation abilities (thus can be a host for a range of biochemical reactions as well), their potential for bioelectronics has been viewed as high. The geometry of the device also has a significant effect on the tissue-like performance and biocompatibility of the device. The tissue-like device geometries, which are usually comprised of flexible filamentary probes, sheet-like architecture, and open-mesh geometries, have been demonstrated to contribute to the chronic stability of bioelectronic implants by reducing mechanical mismatches between nerve cells and bioelectric devices (Figure 1).[17] Second, modifying the surfaces of bioelectronic devices improves their biocompatibility and reduces their inflammatory response.[18–26] Third, self-healing materials have been shown to enhance the efficacy of bioelectronic devices by eliminating the necessity for additional surgery to fix or replace damaged components.[27–30] Finally, new synthetic or fabrication strategies have been developed to create tissue-like materials for neural interfaces. As an example, a 3D-printing system using artificial intelligence algorithms has the potential to optimize the fabrication of "tissue-like" materials in the future.[31]

There have also been recent advances in bioelectronic interfaces with engineered tissues, such as neural organoids, which have attempted to address this mechanical mismatch. A wide range of nano- and micro-structured materials, including flexible filaments, thin membranes, open mesh architectures, stretchable materials, and viscoplastic materials, have shown great promise for improving bioelectronic interfaces with engineered tissues.[32,33] Aside from bioelectronic studies of electrophysiology from engineered tissues, the engineered tissue-embedding 3D electronic hybrid represents an opportunity for implantable bioelectronics that are tissue-like, living, and seamless in their integration with living tissues.

Currently, tissue-like materials do not have a clear definition. We define tissue-like bioelectronics as those which have minimal, or even negligible, mismatches between their bioelectronic components and the target biological tissues. The mismatches may be mechanical, chemical, biological, or even electrical or thermal, but our primary focus in this perspective is on mechanical mismatches, as well as chemical mismatches in some places. In addition, we focus on the development of "tissue-like" materials for neural
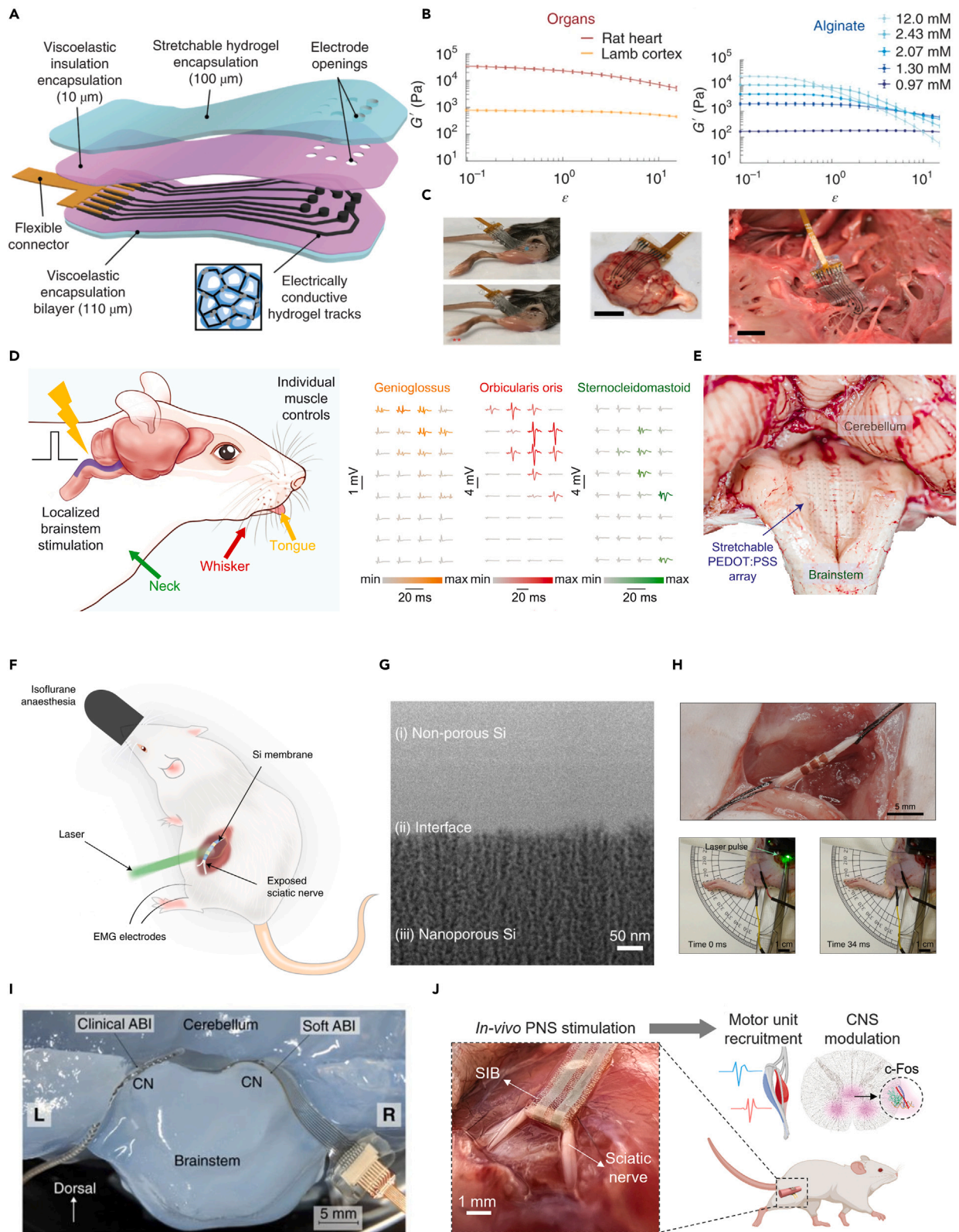
Figure 2. Intrinsically soft materials and soft-hard composites

(A) Schematic of the viscoelastic device and its components.

(B) Comparison of storage moduli between lamb cortical tissue and alginate hydrogels with different concentrations of crosslinking agent. The moduli are a function of strain (ε) at 1 Hz frequency.

(C) The viscoelastic device stimulated the foot of a mouse hindlimb (left), and red asterisks (**) shows the responding portion of the muscle. The device was conformed to a rat cortical surface (middle) and the nerves of a bovine heart (right), scale bars, 3 mm. Reproduced with permission.[40] Copyright 2021, Springer Nature.

(D) Schematic of brainstem stimulation to evoke muscle activities (left), and recorded activities after stimulation (right).

(E) The stretchable device conformed onto the brainstem. Reproduced with permission.[41] Copyright 2022, the American Association for the Advancement of Science.

(F) Schematic of sciatic nerve stimulation.

(G) The STEM image of nanoporous silicon.

(H) Photo-stimulation of hindlimb through the silicon membrane wrapped around the sciatic nerve. Reproduced with permission.[42] Copyright 2022, Springer Nature.

(I) Comparison of the conformability between the clinical ABI and soft ABI. Reproduced with permission.[43] Copyright 2019, the American Association for the Advancement of Science.

(J) The stimulation of the sciatic nerve though strain-insensitive bioelectrodes (SIBs). Reproduced with permission.[44] Copyright 2022, the American Association for the Advancement of Science.

modulation *in vivo* and the interfacing of organoids *in vitro*. We intend to use our discussion of "tissue-like" materials as a springboard for developing advanced tissue-like bioelectronics.

ACHIEVING SIMULTANEOUS DEFORMABILITY AND CONDUCTIVITY

As neural tissue is delicate and susceptible to external interferences, *in vivo* modulation remains challenging because it requires probing stability whereas causing minimal damage to the neural interface. When describing the material's compliance and flexibility, bending stiffness is considered a figure-of-merit for evaluating its resistance to deformation during bending. This characteristic is proportional to a material's Young's modulus, which refers to the material's inherent ability to withstand tensile or compression deformation, as well as to its characteristic feature size (e.g., thickness) in the direction of bending. A reduction in the Young's modulus or feature size of device components can improve mechanical compliance. Typically, the Young's moduli of neural tissues are between 100 Pa and 10 kPa, whereas the Young's moduli of conventional electrodes are many orders of magnitude greater.[18]

Because of their intrinsic low Young's modulus, biocompatibility, and high water and ion content, hydrogels are potential candidates for biomedical applications.[8,34,35] Having similar mechanical properties to biological tissues, hydrogels can be enhanced with conductive polymers[36,37] or nanomaterial fillers[38,39] to enhance their electronic conductivity. For example, alginate hydrogels with varying concentrations of crosslinking agent displayed a similar viscoelastic property with lamb cortex and rat heart, with a modulus ranging from 10 Pa to 100 kPa (Figure 2B).[40] As compared to conventional flexible substrates, such as Ecoflex and polyimide, the alginate hydrogel showed superior conformability, with a two-fold increase in coverage of brain sulci. Graphene flakes and carbon nanotubes were blended in the ionically conductive alginate hydrogel matrix to enhance its electronic performance (Figure 2A). Polydimethylsiloxane (PDMS), which is self-healing and anime-terminated, was covalently conjugated with alginate gel to develop a highly deformable insulation layer. It was shown that the viscoelastic electrode was able to conform to the cortical surface of a rat brain as well as nerves in a bovine heart without causing tissue damage or device dislocation. Different domains of muscle were activated when the electrode was applied to the hindlimb of a mouse (Figure 2C). Recently, a polyrotaxane (PR) structure was incorporated into a supramolecular network with exceptional conductivity and stretchability.[41] The material did not crack under 100% strain, making it highly suitable for applications requiring a high level of mechanical strain. Photopatterning techniques were used to fabricate the material with high precision (Figure 2E). A conformable electrode was applied to the brainstem of mice and used to deliver localized electrical stimulation, allowing precise control of tongue, whiskers, and neck muscle movements (Figure 2D). The results of this study indicate the potential for using this strategy to create advanced neuroprosthetics and other applications which require stretchable, conductive materials with precise patterning capabilities. In general, key factors of developing soft, conformable electronic materials include low bending stiffness, Young's modulus comparable to neural tissues, and reduced feature size. Hydrogels, because of their biocompatibility and low Young's modulus, are promising candidates. Enhancing electronic conductivity with conductive polymers or nanomaterial fillers, and incorporating innovative structures like polyrotaxane, can result in materials with exceptional mechanical and electrical properties.

A

B

C

D

E

F
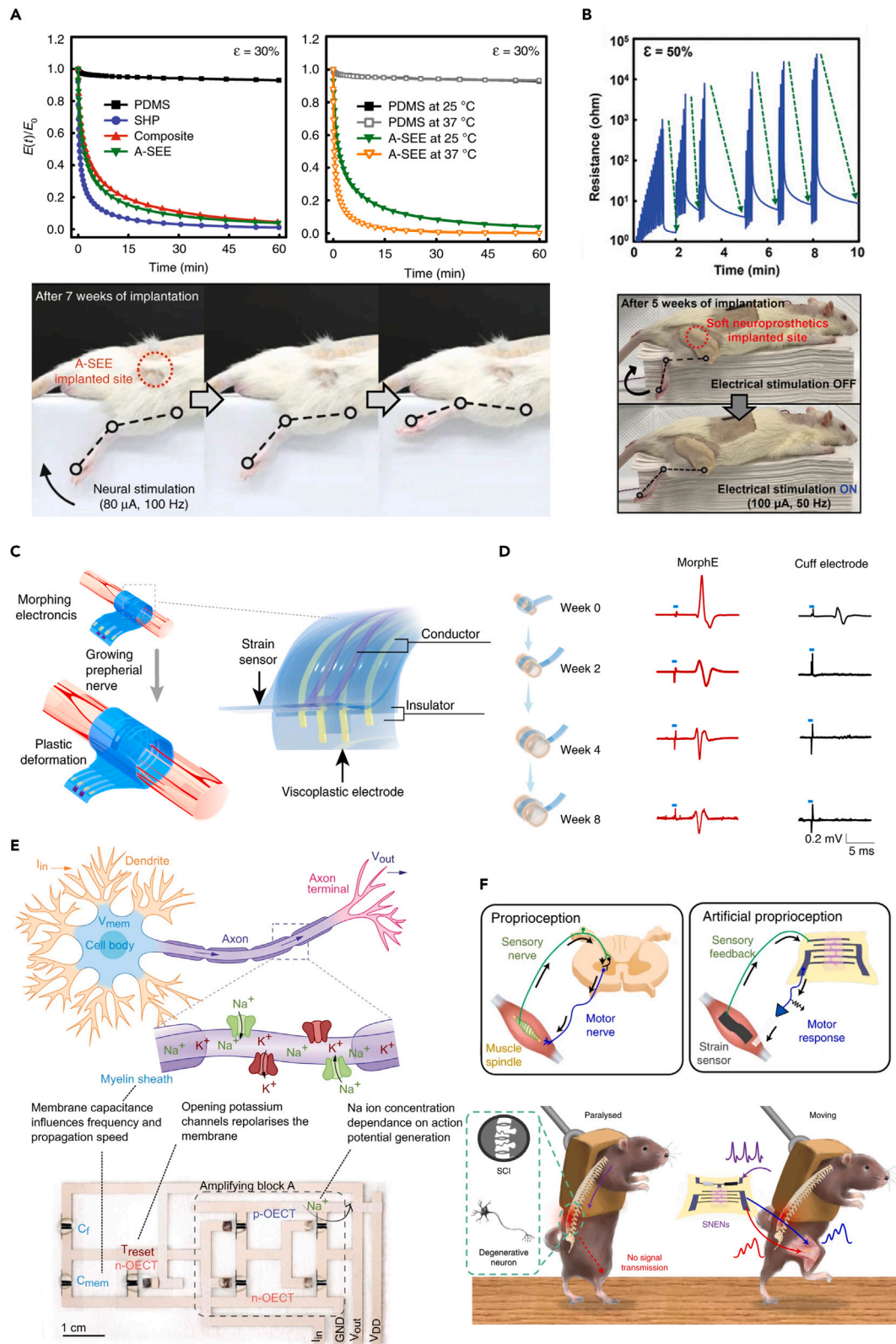
Figure 3. Self-healing and adaptable materials

(A) Normalized tensile stress relaxation of different materials (left) and different temperatures (right) respectively, as a function of time. Electrical stimulation of hindlimb movement (Bottom). Reproduced with permission.[28] Copyright 2020, Springer Nature.

(B) The electrical self-recovery of the material under mechanical deformation cycles (top). The electrical stimulation of hindlimb by neuroprosthetics (bottom). Reproduced with permission.[29] Copyright 2021, John Wiley and Sons.

(C) Schematic of MorphE adapting to the sciatic nerve growth of the rat.

(D) Comparison of evoked compound action potential between MorphE and commercial cuff electrode; the blue dash represents the 200 μs electrical stimulation pulse with amplitude of 300 mV. Reproduced with permission.[49] Copyright 2020, Springer Nature.

(E) Schematic of the circuit design analogous to the biological neurons. Reproduced with permission.[50] Copyright 2022, Springer Nature.

(F) Schematics of artificial proprioception analogous to the biological pathway (top). SNENs helped paralyzed mouse recover voluntary motor function (bottom). Reproduced with permission.[51] Copyright 2022, Springer Nature.

OPTIMIZING SOFT-HARD COMPOSITES

In addition to the development of intrinsically soft and conductive polymers, the reduction of critical dimensions of rigid inorganic materials enhances mechanical compliance and creates additional opportunities. Using a flexible porous silicon membrane, a laser-induced photocurrent can modulate nerve tissue without the need for any interconnects (Figure 2F).[42] Using hydrofluoric and nitric acids, nanoporous/non-porous silicon heterojunction membranes were fabricated (Figure 2G), which can have a thickness of only two micrometers. When supported by PDMS membranes, these ultrathin silicon membranes provide tissue-like bioelectronic interfaces. The membrane was tested *in vivo* on rats and proved to be capable of wrapping around the sciatic nerve without any cracks or adhesives while stimulating the sciatic nerve to move the lower limb in response to pulsed light (Figure 2H). Transdermal stimulation of nerves could be achieved using near infrared light (NIR)-induced photocurrent.[45] Soft hydrogel-based optical fibers may also be used in the future to deliver light to nerve tissues *in vivo* to stimulate them postoperatively.[42] Another example is the new auditory brainstem implants (ABIs) developed to restore hearing in individuals with damaged auditory nerves.[43] Clinical ABIs with rigid electrode paddles can have poor conformity to the cochlear nucleus' small, curvilinear surface. The novel soft and conformable ABI consists of stretchable platinum-silicone electrode contacts and elastic microstructured interconnects (2 μm multilayer of polyimide/platinum/polyimide) (Figure 2I). Chronically implanted soft auditory brainstems were shown to be effective in mice. Both electrically evoked auditory brainstem responses (eABRs) and inferior colliculus neural activity responded strongly to electrical stimulation. One last example involved the manufacture of thin (∼140 μm) and soft (∼10 MPa) electrode films containing silver nanowires.[44] Under strain, this layered thin film was able to maintain stable electrochemical and electrical performances through both in-plane and out-of-plane conductive pathways. This method was applicable to a variety of inorganic materials, such as iridium oxide, gold, and platinum. *In vivo* neuromodulation of the central nervous system and stimulation of the motor muscle unit has been demonstrated (Figure 2J). Soft-hard composites have demonstrated promise, but further research is needed to enhance their performance and reliability, such as refining fabrication techniques for complex structures with high spatial resolution to enable more precise and targeted stimulation of the nervous system.

ENABLING SELF-HEALING BEHAVIOR

The neural tissue is subjected to mechanical stresses during normal function and during implantation. Given that making neural implants softer is required to reduce mechanical mismatches between implants and neuronal tissues, devices made of softer materials would be more fragile and sacrifice the robustness to some extent. In this way, rigid and sharp surgery tools to handle these delicate devices could pose great threats to the device integrity and functionalities. What's more, during normal functions or when encounter impacts, neural tissues will exhibit forces that could damage delicate bioelectronic implants. More specifically, nerves could be compressed externally by approximation to adjacent tissues, such as muscle, tendon, or bone, or by pressure increases in the extraneural environment.[46] Common functional positions may result in normal stress in a level of 10^3 Pa and in the case of environmental impact, it can reach 10^4 Pa. For a peripheral nerve, it could move several centimeters relative to the surrounding tissues and bones which should be induce forces large enough to trigger damage when the implanted device is soft enough.[47] In central nervous system, on impact, maximum shear stress imposed on neural tissues such as brain stem and corpus callosum could reach up to 10^5 Pa.[48] The inability of a bioelectronic material to repair itself after such mechanical damage may lead to a loss of its functional properties such as conductivity or mechanical strength. Consequently, neural modulation devices may be less effective. Furthermore, self-healing materials may reduce the need for surgical intervention to repair or replace damaged materials, which can be time-consuming, costly, and invasive. An adaptive, self-healing electronic epineurium (A-SEE) has been developed using a dynamically crosslinked and tough

self-healing polymer (SHP) matrix.[28] This material is capable of efficiently dissipating the strain energies induced by muscle contraction and relaxation, as well as nerve stretching and twisting (Figure 3A). In this way, the devices can be protected from irreversible damage during implantation. For a period of seven weeks, a robust A-SEE device was shown to deliver neural stimulation to the rat sciatic nerve (Figure 3A). Moreover, the same group has developed a fatigue-resistant neuroprosthetic device made from a nanocomposite containing gold nanoshell (AuNS)-coated silver flakes dispersed within a self-healing polymer matrix.[29] Because of its self-healing characteristics, the coated flakes were able to rebuild their percolation networks after degradation, thus restoring their electrical and mechanical performance after being subjected to intense deformations (Figure 3B). With the application of electrical stimulations, the device was able to effectively stimulate both tetanic and twitch muscle contractions in the sciatic nerve (Figure 3B). Nerve coaptation, or the surgical repair of damaged nerves, is a crucial step in the treatment of nerve damage. Self-healing polyurethane elastomers (SHEs) have been developed as an alternative to traditional sutures.[30] The SHEs showed superior performance compared to normal sutures in repairing a sciatic nerve cut. These SHEs may improve outcomes for patients with nerve damage by stimulating the rebuilt nerve. By choosing materials with innate self-healing capabilities and designing cross-linking strategies, such as dynamic covalent bonds (e.g., disulfide, Diels-Alder, or boronic ester bonds), designers can create bioelectronic devices with enhanced reliability and functionality. These materials should balance mechanical flexibility and robustness, exhibit responsiveness to specific stimuli, and ensure biocompatibility to minimize adverse biological responses, whereas maintaining desired electrical properties for target applications. Future research could also focus on developing self-healing materials that can repair damage both at the macroscopic and nanoscale, where many critical electrical and mechanical properties are generated.

IMPROVING ADAPTABILITY

As materials become more adaptable and tunable, they can be adapted to a variety of different scenarios. Currently, most bioelectronic materials are fixed in shape or dimension so they cannot accommodate developing neural tissue. This would gradually exert mechanical stress on growing tissues, requiring repeated traumatic interventions. A new type of growth-adaptive morphing electronics (MorphE) has been developed that can take into account the growth of soft tissue.[49] In the MorphE, a viscoplastic conductive polymer and a self-healing insulating polymer are used (Figure 3C). With a mechanical response based on strain rate, these materials can deform at a rate similar to soft tissue's growth rate, but can also withstand increased stress caused by undesired morphology changes when fast body movement is used. A morphing electronic system was wrapped around the sciatic nerve of fast-growing rats. As nerve diameter increased by 2.4-fold, the electrodes remained effective and demonstrated more stable chronic electrical stimulation than commercial cuff electrodes (Figure 3D).

In addition, neuromorphic systems, which are designed to mimic the functionality of biological neural networks, provide the ability to target specific neural circuits with greater accuracy and to modulate them more effectively with the potential for real-time adaptation and learning. One such example is the design of the first all-printed complementary organic electrochemical transistors (OECTs) (Figure 3E).[50] The OECNs exhibited neuronal characteristics such as ionic concentration-dependent spiking, and were used to modulate the lobe closure of Venus flytraps. When the input current was increased to 10 μA, the flytrap closed, although it did not close at a low input current of 2 μA to the artificial neuron. A future application of these OECNs in vertebrates may open up new possibilities for neuromodulation therapies. In a recent study, it was demonstrated that a stretchable neuromorphic efferent nerve (SNEN) can be utilized to bypass impaired nerve pathways in spinal cord injury (SCI) and motor neuron disease (MND).[51] SNEN was composed of organic nanowire synaptic transistors, carbon nanotube strain sensors, and hydrogel electrodes. By working together, these components reproduced the electrophysiological signaling that normally occurs within the nervous system, enabling the modulation of muscle movement (Figure 3F). The study also reported the successful activation of bipedal walking locomotion in a paralyzed mouse, providing evidence that this technology could potentially be used to treat individuals with SCIs and MNDs. Such stretchable neuromorphic devices utilizing organic materials represent a promising development in the field of neuroprosthetics.

To ensure accurate implant insertion and protect soft tissue at the same time, adaptable material moduli can be beneficial. A rigid probe can be implanted directly, but can damage the nerve tissues and trigger an inflammatory response because of the mismatch between the probe and the tissue. The tissue-like soft probes, on the other hand, cause less damage, but they require special implantation procedures. In one study, microfiber-shaped neural probes incorporating carbon nanotube fibers as electrodes and calcium ion crosslinked sodium

alginate shells have been demonstrated to exhibit sufficient stiffness when they are implanted.[52] After implantation, they changed their elastic properties when exposed to water, becoming soft and similar to brain tissue in stiffness (Figures 4C and 4D). The fabrication of materials with fully tunable moduli while achieving bidirectional sensing and modulation functions might be a potential future direction. A recent study sheds light on this direction by integrating multiple functions into hydrogel probes that possess adaptive bending stiffness depending on the level of hydration.[54] To achieve sensing, modulation, and drug delivery, optical, electrical, and fluidic fibers were assembled into the hydrogel matrix (25 μm). Dry hydrogel penetrated brain tissue easily and became softer and more compliant when hydrated (Figure 4E). Because the modulus of the hydrogel cannot be precisely tuned based on hydration levels, it is limited to being used in tissues and models with different conformability and stiffness requirements. A more precise microfabrication technique would also enhance the signal resolution by miniaturizing the current device.

PRODUCING BIOACTIVE SURFACES

The implantation of bioelectronics devices has been found to trigger a neuroinflammatory response. The activation of microglia and the release of inflammatory cytokines lead to neuronal loss and the formation of astroglial scar. This process not only causes damage to the surrounding tissue but also increases the impedance of the device, which can significantly lower its performance.[55] The utilization of advanced strategies to enhance biocompatibility and mitigate neuroinflammation is a crucial area of research within the field of neuroprosthetics. These strategies include the application of anti-inflammatory or neuron-promoting coatings,[19] such as alpha melanocyte-stimulating hormone,[20] dexamethasone,[21] interleukin-1 receptor antagonist,[22] and laminin.[18,23] A recent study employed a brain-derived neuronal adhesion molecule, L1, to coat neural electrodes at 16 weeks post-implantation in a murine model, resulting in increased axonal and neuronal density and decreased gliosis.[24] Another study utilized extracellular matrix (ECM) coating derived from primary rat astrocytes to modulate immune responses, with the astrocyte-derived coating demonstrating the ability to inhibit macrophage activation.[25] Upon implantation in the rat cortex, this coating reduced astrogliosis without significant impact on macrophage activation or neuronal survival, or changes in the intensity or distribution of foreign body response biomarkers. In addition, synthetic materials such as poly(sulfobetaine methacrylate) (PSBMA), a zwitterionic polymer coating, have been shown to inhibit nonspecific protein adsorption and attachment of inflammatory cells.[26] In the future, these surface modification strategies may be integrated with tissue-like material designs to further improve tissue-like characteristics. However, further clinical trials are necessary to assess the safety and effectiveness of these surface-modified electrodes in various neurological disorders, providing insight into their potential applications and limitations.

ACHIEVING STRUCTURAL COMPLEXITY

The fabrication of soft and soft-hard materials through printing and patterning is critical for the creation of intricate tissue-like structures. Conventional inkjet printing methods, however, are limited by feature sizes greater than 100 μm, resulting in a lack of resolution and structural vulnerability. In addition, traditional lithographic micropatterning techniques are not suitable for materials with high water content. To overcome this challenge, researchers have developed an electrically conductive hydrogel (ECH) that can be micropatterned using traditional lithographic methods, with a resolution of 5 μm or higher.[53] This ECH is created by lithographically micropatterning an electrode array, utilizing an Au hard mask, onto a poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) gel filled with an ionic liquid. The ionic liquid is then replaced with water to produce a micropatterned electrically conductive hydrogel (MECH) film that exhibits high conductivity and a low young's modulus of approximately 30 kPa. To ensure reliable neural tissue compliance and stable electrical performance, UV-crosslinked dimethacrylate-functionalized perfluoropolyether insulation layers (PFPE-DMA) are photopatterned over the hydrogel electrode, resulting in a young's modulus less than 30 kPa (Figures 4A and 4B). This device can then be utilized to deliver localized electrical pulses and stimulate leg and toe movement in mice, through intimate contact with the exposed sciatic nerve, with a voltage as low as 50 mV.

LEVERAGING ORGANOID MODELS

Neuronal organoids, as advanced three-dimensional *in vitro* neural constructs derived from human induced pluripotent stem cells, represent a highly promising area of research because of their capacity to replicate key anatomical and functional characteristics of human nervous systems.[56–59] Owing to their small sizes (typically measuring in millimeters or sub-millimeters), softness, and three-dimensional geometries, these *in vitro* neuronal organoids necessitate the integration of tissues-like properties, such as flexibility and softness, in interfacing bioelectronics to fully realize their potential.[60–65]
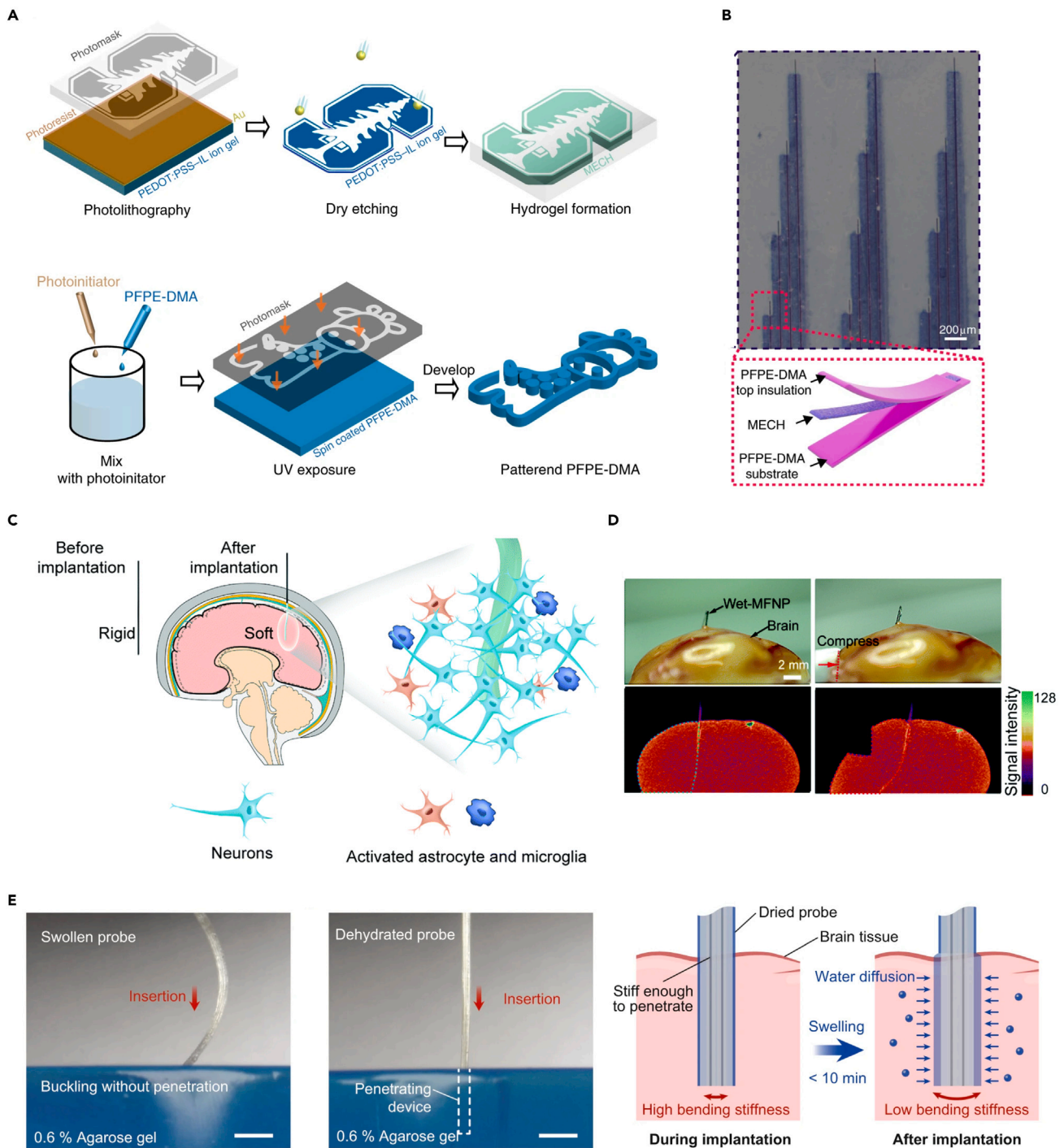
**Figure 4. Implantation and fabrication of materials**

(A) Schematics of lithography process of the MECH (top) and the PFPE-DMA layer (bottom).

(B) Assembled MECH electrodes with encapsulation layers. Reproduced with permission.[53] Copyright 2019, Springer Nature.

(C) Schematic of the modulus change of the neural probe before and after implantation.

(D) Implanted neural probe inside a mouse brain before and after compression, photograph (top) and micro-CT images (bottom). Reproduced with permission.[52] Copyright 2013, Royal Society of Chemistry.

(E) Illustrations of the insertion of fully swollen and dehydrated hydrogel probes into the phantom brain (0.6% agarose). Reproduced with permission.[54] Copyright 2021, Springer Nature.
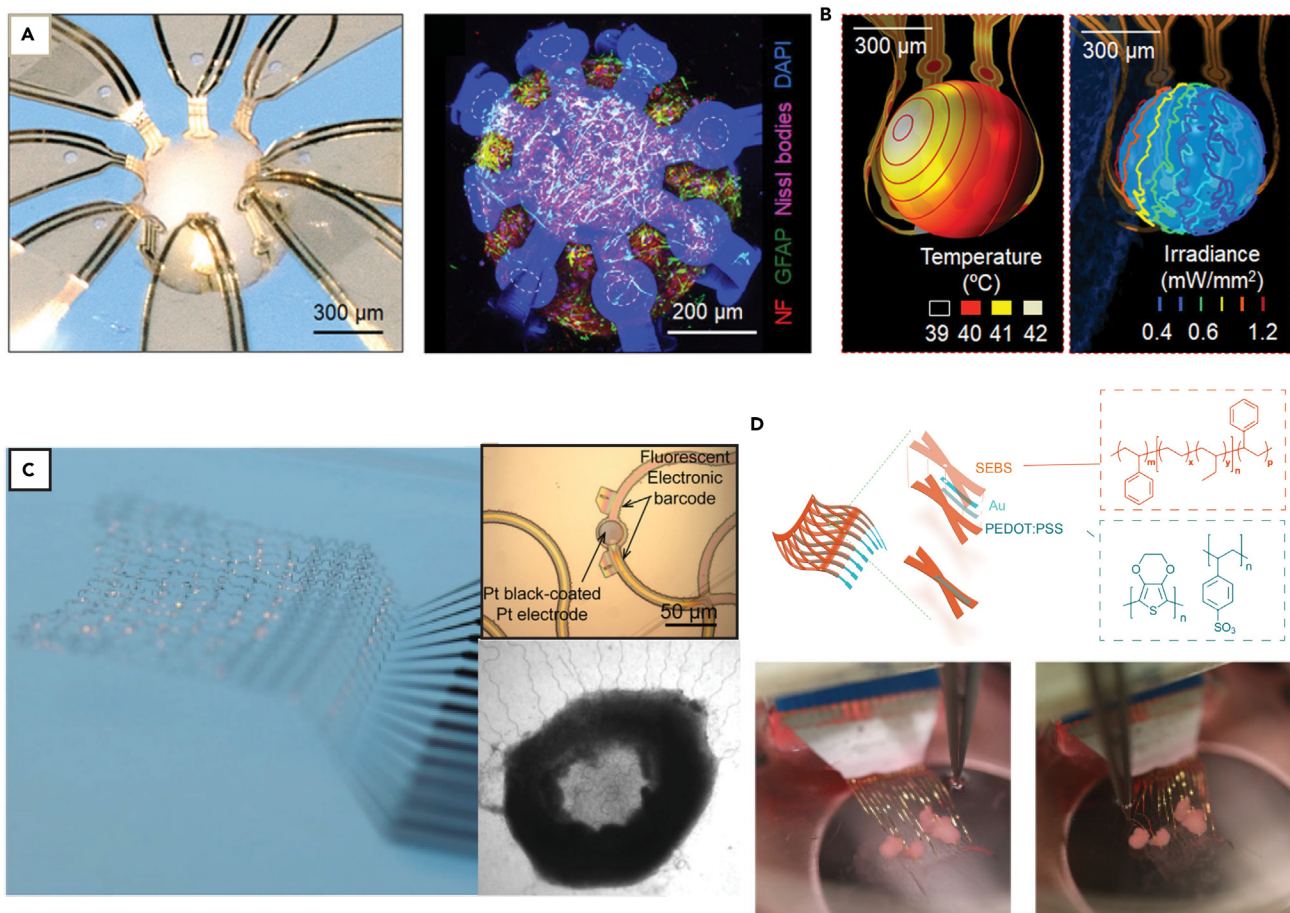
Figure 5. Tissue-like bioelectronics for organoid integration

(A) Optical image (left) and confocal microscope image (right) of the 3D assembled device enveloping a neural organoid.

(B) Computed 3D spatial distribution of temperature (left) and light intensity (right) generated by integrated modulation modules. Reproduced with permission.[62] Copyright 2021, the American Association for the Advancement of Science.

(C) Optical image of stretchable mesh electronics, the zoom-in view of a single Pt electrode coated with PEDOT (upper right), and optical image neural organoid integrated with stretchable mesh electronics (lower right). Reproduced with permission.[64] Copyright 2022, John Wiley and Sons.

(D) Intrinsically stretchable mesh electronics schematics and the materials design. Reproduced with permission.[65] Copyright 2022, Elsevier.

The integration of organoids with bioelectronic devices requires the utilization of flexible materials and structures to ensure a seamless interface. To accomplish this, a novel methodology of unfolding-integration-folding was employed to create 3D geometries that delicately envelop the organoids and establish robust interfaces. The degree of flexibility can be precisely adjusted through the manipulation of device thickness[60,61] and crosslinking.[61] The development of a multifunctional, flexible 3D framework for the on-demand modulation of neural organoids has been achieved (Figure 5A).[62] The 3D geometry of the device, characterized by a pouch-like "cage," was generated through a process of controlled buckling. The low bending stiffness of the wings, at 7.9×10^{-12} N m^2, enables the formation of a tissue-like mechanical framework that effectively interfaces with the organoid. The device is equipped with a plethora of modulation modules, including a thermal actuator capable of inducing heat stress up to 50°C and a blue LED for localized optogenetic neural modulation (Figure 5B).

The formation of organoids, or organogenesis, is a complex and dynamic process that involves a 2D-3D transition, providing a unique opportunity for the integration of bioelectronic devices without the need for late-stage insertions. These devices can seamlessly "grow" with the cells and ultimately become an integral part of the organoid during the integration process.[63–65] To achieve this, the devices must possess a sufficient level of softness to facilitate the manipulation of cell-cell attraction forces. To this end, mesh electronics platforms were developed, featuring low thickness and sub-cellular-size components, resulting in an effective

Table 1. Comparison of modulus between recent developed materials and targeted natural tissues

Interfacing materials	Young's modulus (E)	Target natural tissue
Alginate hydrogels[40]	1.0×10^2 to 1.0×10^5 Pa (Storage modulus G')	Cortex: 1.0×10^3 Pa Heart: 1.0×10^4 Pa
Polydimethylsiloxane (PDMS)[41,42]	3.6×10^5 to 8.7×10^5 Pa	Brainstem: 1.9×10^3 Pa[66] Sciatic nerve: 2.3×10^2 Pa[67]
PDMS + Microstructured polyimide/platinum/polyimide[43]	3.0×10^6 to 4.0×10^6 pa	Brainstem: 1.9×10^3 Pa
Silver nanowire (AgNW) + Poly (urethane acrylate) (PUA) + anisotropically conductive film (ACF)[44]	1.0×10^7 Pa	Sciatic nerve: 2.3×10^2 Pa
Self-healing polymer (SHP)[28]	1.6×10^5 Pa	Sciatic nerve: 2.3×10^2 Pa
Self-healing elastomer (SHE)[30]	1.7×10^5 to 3.7×10^6 Pa	Sciatic nerve: 2.3×10^2 Pa
Viscoplastic polymer[49]	4.0×10^5 Pa	Growing sciatic nerve: 1.3×10^2 to 2.3×10^2 Pa[67]
Microfiber-shaped neural probes (MFNPs)[52]	1.0×10^4 Pa	Brain tissue: 3.0×10^3 Pa
Poly(acrylamide)-alginate (PAAm-Alg) hydrogel[54]	1.7×10^4 Pa	Brain tissue: 3.0×10^3 Pa
Electrically conductive hydrogel (ECH)[53]	1.9×10^4 to 3.7×10^4 Pa	Sciatic nerve: 2.3×10^2 Pa

bending stiffness of 6.7×10^{-16} N m^2.[64] This feature, in combination with the brain-matching mechanical properties of mesh electronics, enables their seamless integration and adaptation to changes in volume or morphology (Figure 5C). In addition, the use of intrinsically soft and stretchable materials has been explored as a means of creating tissue-like bioelectronic systems. A demonstration of this was achieved using a poly(-styrene-ethylene-butylene-styrene) (SEBS)-based device with a special mesh geometry and an elastic poly(sty-rene-ethylene-butylene-styrene) hydrogel (Figure 5D).[65] Furthermore, electrical modulation capability was demonstrated following the successful integration of the device with brain organoids (Figure 5D).

The field of organoid bioelectronics is experiencing exponential growth as the integration of tissue engineering and electrical engineering techniques yields the development of functional bioelectronic devices. This emerging paradigm of translational medicine holds the potential for utilization in various applications, including drug efficacy testing, modulation of cellular activity, and modeling of pathological conditions. In addition, the utilization of organoid bioelectronics in the development of brain-machine interfaces represents a promising avenue for future research.

CONCLUSION AND OUTLOOK

The integration of bioelectronic devices with biological tissues remains a significant obstacle in the field of bioelectronics. Utilizing *in vivo* animal models, various techniques have been employed to fabricate materials that exhibit mechanical (Table 1) and (bio)chemical characteristics comparable to the targeted tissue. To gain a deeper understanding of human-scale biological systems, scientists have developed organoids and investigated devices that can be encapsulated or integrated within three-dimensional organoids. Despite these advancements, there are still several areas that require further investigation.

The utilization of personalized bioelectronic implants, tailored to specific anatomical structures and experimental models, is crucial for optimal biological modulation. Utilizing robotic inkjet technology, the rapid prototyping of soft electrode arrays, composed of conductive ink containing platinum microparticles and silicone elastomers, was achieved (Figure 6A).[68] The mechanical properties of the electrodes were comparable to that of soft tissue, enabling adaptability to varying tissue anatomy. Through the use of electrical spinal cord stimulation in decerebrated felines, activation of flexor and extensor muscles leading to hindlimb movements was observed (Figure 6B). Further research is necessary to determine the long-term performance and reliability of these customized neural implants. In addition, the potential enhancement of these implants through integration with other technologies, such as drug delivery systems or optogenetics, should be explored.
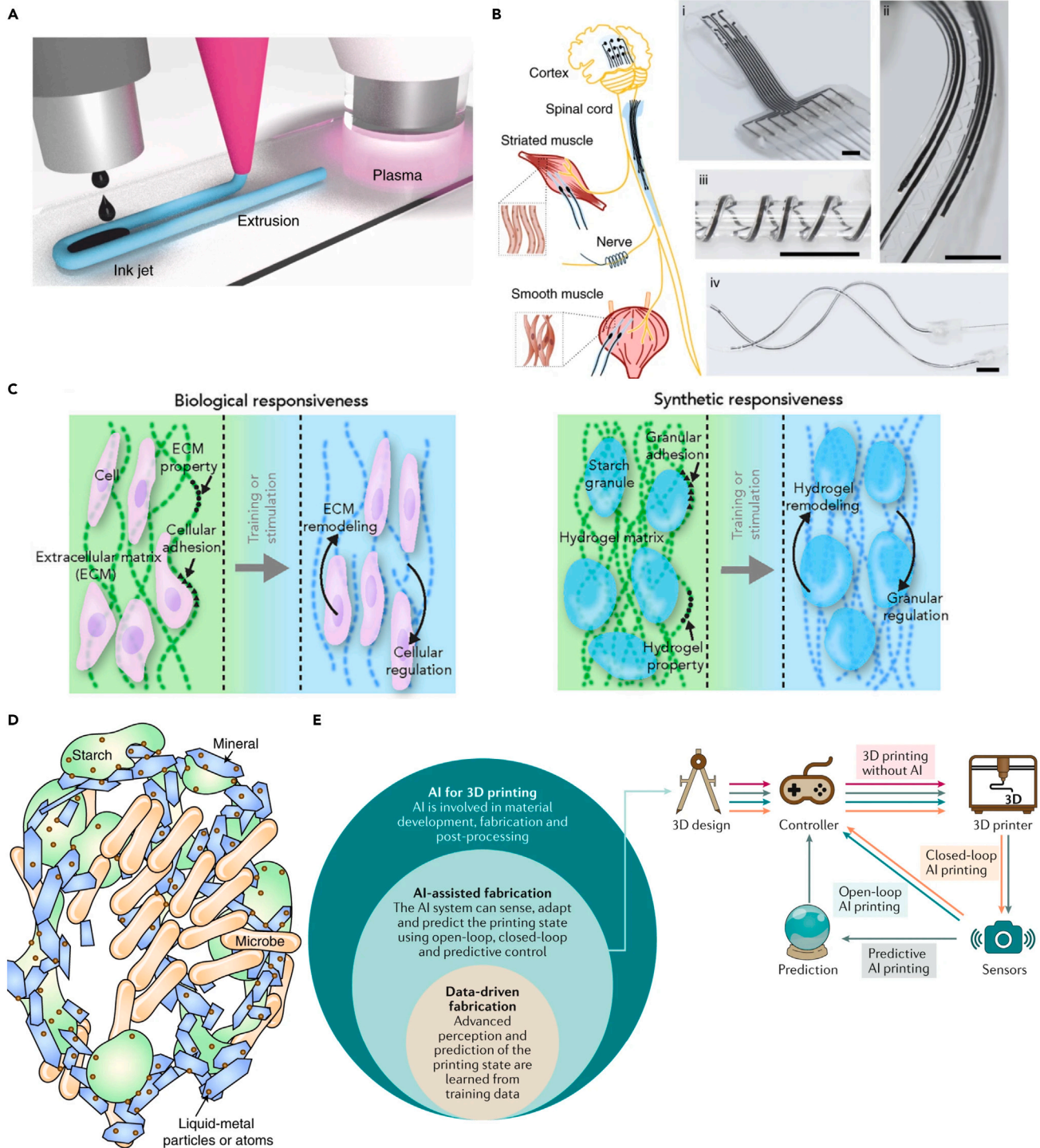
Figure 6. Future research directions

(A) Illustration of robotically controlled inkjet to rapid prototype customized soft electrode arrays.

(B) Different electrode morphologies for different tissue anatomies, such as (i) cortical surface electrode array, (ii) spinal surface electrode array, (iii) peripheral nerve monopolar electrode, and (iv) intramuscular shank electrodes, scale bars, 4 mm. Reproduced with permission.[68] Copyright 2020, Springer Nature.

C) Starch granule composite hydrogel mimic biological tissues regarding structures and properties. Reproduced with permission.[69] Copyright 2020, Elsevier.

(D) Schematic of a microbial system incorporated into the soil-inspired material. Reproduced with permission.[70] Copyright 2022, Springer Nature.

(E) Schematic of AI-involved fabrication workflow. Reproduced with permission.[31] Copyright 2020, Springer Nature.

In the realm of material design, the majority of strategies center around aligning modulus or stiffness with soft tissue properties. However, few take into account the cellular-level building blocks that make up these tissues. To address this gap, researchers have utilized rigid materials, such as semiconductor nanowires, to achieve cellular or sub-cellular interfaces.[11] Through the fabrication of three-dimensional electronic networks that mimic neuron structure and mechanical properties, devices have been developed that possess a bending stiffness that is 5–20 times less than conventional probes.[71] These devices are constructed from a polymer/metal/polymer structure with a thickness of 0.9 μm, and feature a thin layer of polymer insulation that mimics the myelin sheath. This allows for stable recording and stimulation of individual cells. However, to create fully tissue-like bioelectronics, materials with more complex tissue-like properties, such as non-linear mechanical behaviors, are needed. A recent study has taken a new approach to synthesizing tissue-like materials by using a polyacrylamide/alginate hydrogel matrix as a mimic for extracellular matrix (ECM) and hydrated starch granules as a model for cells (Figure 6C).[69] This composite material, incorporating cell-like starch granules measuring ∼10 μm, possesses self-healing, impact-absorbing, stress-stiffening, and programmable mechanical properties. Although no bioelectronic performance has yet been demonstrated, this research presents a promising new avenue for creating multiscale tissue-like systems that mimic both cells and extracellular matrix. In addition, the concept of "living materials" has emerged, which incorporates living components such as bacteria to create a tissue-like biological modulation platform. These living systems have the potential to exhibit superior responsive behavior compared to fully synthetic systems (Figure 6D).[70]

Through computer simulations, we will be able to study the behavior and performance of tissue-like materials and adjust their properties accordingly.[72] The simulations can help us understand the effects of the material on the tissue and the stimuli, and can be useful in optimizing the material's design and properties. The integration of artificial intelligence (AI) and robotics has the potential to revolutionize the production of tissue-inspired materials for biological modulation.[31] Utilizing AI algorithms to govern and optimize the performance of robotic systems during the fabrication process can yield structures with specific properties, such as mimicking the stiffness, conductivity, or even the biochemical characteristics of specific tissues (Figure 6E). The utilization of robotics in laboratory settings allows for precise deposition and patterning of materials on micro and nanoscales, thus automating the creation of tissue-like materials. This can result in the generation of more intricate and accurate structures that emulate the complexity of natural tissues.

AUTHOR CONTRIBUTIONS

C.S. and Z.C. conceived the theme and designed the manuscript structure. C.S., Z.C., and J.A.H. wrote the manuscript. B.T. supervised this work and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

INCLUSION AND DIVERSITY

We support inclusive, diverse and equitable conduct of research.

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