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Bioresorbable neural interfaces for bioelectronic medicine

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Bioresorbable neural interfaces have the potential to significantly advance the treatment of neurological disorders and modulate the nervous system, as they can safely degrade into biologically benign end products after a specified operational period without requiring additional surgical interventions. In this review, we present a comprehensive overview of recent developments in bioresorbable neural interfaces, including electrical, optical, electrochemical, mechano-electric, thermal, and magnetoelectric strategies for neuromodulation and regenerative medicine. Associated material options, fabrication techniques, and therapeutic applications will be discussed.

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Introduction

Implantable neural interfaces, serving as a critical medium to probe and modulate the nervous system [1], have been leveraged to mitigate neurological disorders [2], alleviate chronic pain [3], and facilitate function restoration following traumatic injuries [4]. Conventional neural interfaces are typically made from nonbiodegradable materials [5], necessitating complex surgical removal after use if they are not designed for long-term applications, which poses additional risks for infection and increases hospital costs. In addition, potential tissue damage can occur during the retrieval process due to fibrotic encapsulation at the implantation site, a common issue arising from foreign body reactions, which further complicates the procedure [6,7]. Recent developments in bioresorbable materials and device platforms could offer potential solutions [8]. These innovations enable the construction of neural interfaces that can completely degrade into biologically benign end products after the operational period, thereby eliminating material retention and obviating the need for secondary surgeries.

In this review, we focus on recent advancements in bioresorbable neural interfaces for neuromodulation and regenerative medicine. We will underscore material strategies, fabrication techniques, biocompatibility, and associated therapeutic applications. The review highlights bioresorbable neural interfaces in five aspects, including electrical interfaces, optical interfaces, interfaces based on electrochemical reactions, mechano-electric interfaces, and other interfaces (thermal interfaces and magnetoelectric interfaces). The advantages and limitations of specific bioresorbable neural interfaces discussed in the review are summarized in Table 1, in terms of different material options, fabrication techniques, and operation mechanisms. For electrical stimulation of peripheral nerve repair, the most frequently used parameters are 0.5−5 mA range, 50−400 μs, and 1−20 Hz [9]. To realize reliable pain blockade, the application of kilohertz frequency alternating current (10 Vpp, 25 kHz) is adopted for a time period that meets clinical needs, and the duration of each stimulus event can be minutes to hours per day [10]. In optogenetic neural interfaces, red or near-infrared (NIR) light (wavelength: 600−1350 nm) enables deeper tissue penetration, and green light in the 490−580 nm range can be used for photovolumetric pulse wave tracing [11]. Future perspectives will be discussed at the end to envision future directions in this field.

Bioresorbable electrical neural interface

As nervous systems operate through electrical impulses for signal transmission, electrical neural interfaces

Table 1

Advantages and limitations of various bioresorbable neural interfaces based on different material options,fabrication techniques, and operation mechanisms.

Interface	Material	Fabrication techniques	Operation mechanisms	Advantage	Limitation	Reference
Conductive conduits	GelMA, ECM, PLLA SiP@PDA, Si, PCL, Mo	Chemical synthesis, drop-casting	Microenvironment regulation	Ease of deployment	Controllability	[13–15]
Electrical interfaces	PLGA, PA, PCL, b-DCPU Mo, Mg,	Laser-cutting	Electrical stimulation	Versatile stimulation modes	Wired connection Miniaturization	[3,15–17]
Optical interfaces	PLGA, PET, PLLA-PTMC, Si, Mo lipid-coated polydopamine	Micro-Nano fabrication	Optical stimulation Optoelectrical stimulation	Remote stimulation	Operational time frame Penetration depth	[19–22]
Electrochemical reaction-based interfaces	Mg, Fe, Mn, Zn	Drop-casting, magnetron sputtering	Self-powered systems through electrochemical reactions	Ease of deployment	Controllability Operational time frame	[25,27]
Mechano-electrics interfaces	PHBV, PLLA, KNN, PDA, ChCl, PEG, PHB	Electrospinning	Piezoelectricity or triboelectricity induced by ultrasound or body movement	Penetration depth Ease of deployment	Ultrasound alignment Implantation site limitation	[29–31]
Other interfaces	POC, PLGA, PFP, magnetoelectric nanoparticles	Laser-cutting, electrospinning	Thermal interface Magnetoelectric stimulation	Local temperature modulation Versatile shapes, remote stimulation	Tethered connection Miniaturization	[32,33]

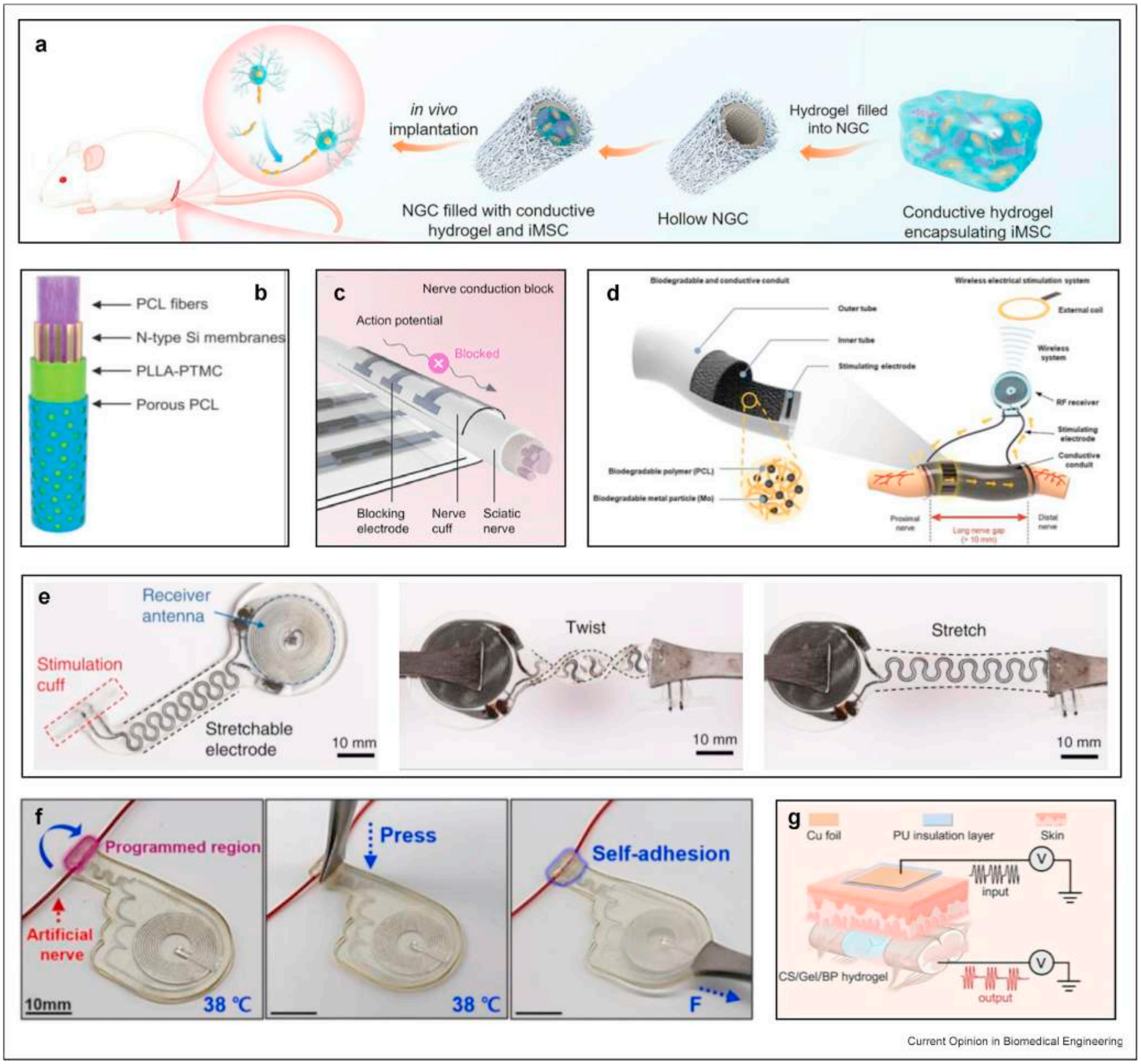
represent the most prevalent method to modulate neurological disorders and restore impaired functions after nerve injuries [12]. Strategies include the use of biodegradable conductive materials to enhance endogenous electric fields, bioresorbable electrodes connected to external power sources for direct electrical stimulation, and inductive or capacitive coupling platforms built with degradable materials to achieve wireless neural modulation.

Biodegradable conductive materials can create electroactive microenvironments that facilitate nerve regeneration. Chao Xu et al. have proposed a biodegradable conductive hydrogel consisting of polydopamine-modified silicon phosphorus (SiP@PDA) nanosheets, methacryloyl gelatin (GelMA), and decellularized extracellular matrix (ECM), as illustrated in Figure 1a [13]. Nerve conduits incorporating the conductive hydrogel material and stem cells promoted tissue repair of injured sciatic nerves. Moreover, Pengcheng Sun et al. have reported fully biodegradable conductive nerve scaffolds that accelerated tissue regrowth and motor functional recovery in rodents with sciatic nerve injuries (Figure 1b) [14]. The scaffold was comprised of conductive N-type silicon (Si) membranes on a multilayer polymeric conduit, which simultaneously offers topological guidance and improved endogenous electrical cues. The beneficial effects of N-type Si membranes include the enhancement of calcium activity of dorsal root ganglion (DRG) neurons and the stimulation of cell proliferation and associated neurotrophic factors of Schwann cells.

In contrast to conductive materials that exploit endogenous bioelectric signals, the use of external electric fields can further improve therapeutic efficacy. For example, Geumbee Lee et al. have developed a bioresorbable nerve stimulator based on molybdenum (Mo) electrodes for pain mitigation (Figure 1c) [3]. The nerve stimulator was fabricated on a poly (lactic-co-glycolic acid) (PLGA) substrate with two layers of polyanhydride (PA) as the encapsulation, and was connected to external equipment to deliver kilohertz frequency alternating current for electrical nerve block.

To eliminate wired connection, Jio Kim et al. proposed a wireless electroceutical platform for nerve regeneration integrating a fully biodegradable conductive nerve conduit with a wireless electrical stimulator based on inductive coupling [15], as shown in Figure 1d. The biodegradable conductive nerve conduit consisted of an outer layer made of a polycaprolactone (PCL) film and an inner layer made of molybdenum microparticles and PCL. Utilizing radiofrequency (RF) electromagnetic waves, the wireless electrical stimulator delivered precise and controllable stimulation to the nerve defect via the biodegradable CNC, and accelerated axonal growth was achieved. Furthermore, Yeon Sik Choi et al. have reported a fully bioresorbable wireless stimulator utilizing

Figure 1



Bioresorbable electrical interface. (**a**), The multifunctional hydrogel for peripheral nerve repair. Reproduced with permission [13]. Copyright 2023, Wiley-VCH. (**b**), A bioresorbable and conductive nerve conduit for neuroregenerative medicine. Reproduced with permission [14]. Copyright 2023, Wiley-VCH. (**c**), A bioresorbable electrical stimulator for nerve conduction block. Reproduced with permission [3]. Copyright 2022, The Authors. (**d**), A biodegradable conductive conduit and a wireless electrical stimulator for nonpharmacological peripheral nerve regeneration. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License [15]. Copyright 2023, The Authors. (**e**), A long-lived, stretchable, and wireless bioresorbable electrical stimulator to enhance recovery from peripheral nerve injuries. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License [16]. Copyright 2020, Springer Nature. (**f**), Stretchable, fully biodegradable, shape transformation wireless electrical stimulation system for nerve injury recovery. Reproduced with permission [17]. Copyright 2024, Elsevier. (**g**), Wireless electrical stimulation based on conductive and biodegradable hydrogels for spinal cord repair. Reproduced with permission [18]. Copyright 2024, Wiley-VCH.

inductive coupling for neuromuscular regeneration (Figure 1e) [16]. The device consisted of a bilayer loop antenna made of Mo dual coils, a stretchable bioresorbable dynamic covalent polyurethane (b-DCPU) that served as the substrate, dielectric interlayer and biofluid barrier, and an RF rectifying diode constructed from doped monocrystalline silicon membranes. The use of serpentine interconnects and b-DCPU endowed the device with excellent stretchability and twistability. The output performance showed no obvious difference under stretching (0−35 %) and twisting (0−360°) conditions. The wireless stimulator showed promise to minimize muscle atrophy following nerve injuries. Moreover, Jun Hyeon Lim et al. integrated a biodegradable, adhesive, and shape-programmable polymer based on poly (L-lactide-co-ε-caprolactone) (PLCL) with the wireless electrical nerve stimulator (Figure 1f) [17]. This synthetic polymer material allowed self-rolling around artificial nerves at approximately 38 °C and achieved secure adhesion. This feature could facilitate convenient and suture-free deployment of the wireless electrical stimulator.

Additionally, wireless exogenous electrical stimulation can also be introduced based on a capacitive coupling method. As shown in Figure 1g, Ping Wu et al. developed a biodegradable conductive hydrogel composed of black phosphorus nanosheets and chitosan/gelatin hydrogel matrix, to provide wireless electrical stimulation through capacitive coupling to promote functional recovery of spinal cord injury (SCI) [18]. By placing a soft metal foil (the power-transmitter electrode) on top of the SCI site, the biodegradable conductive hydrogel can act as the power-receiver electrode, thereby enabling controllable alternating current to promote tissue regeneration through electrostatic induction effects.

Bioresorbable optical neural interfaces

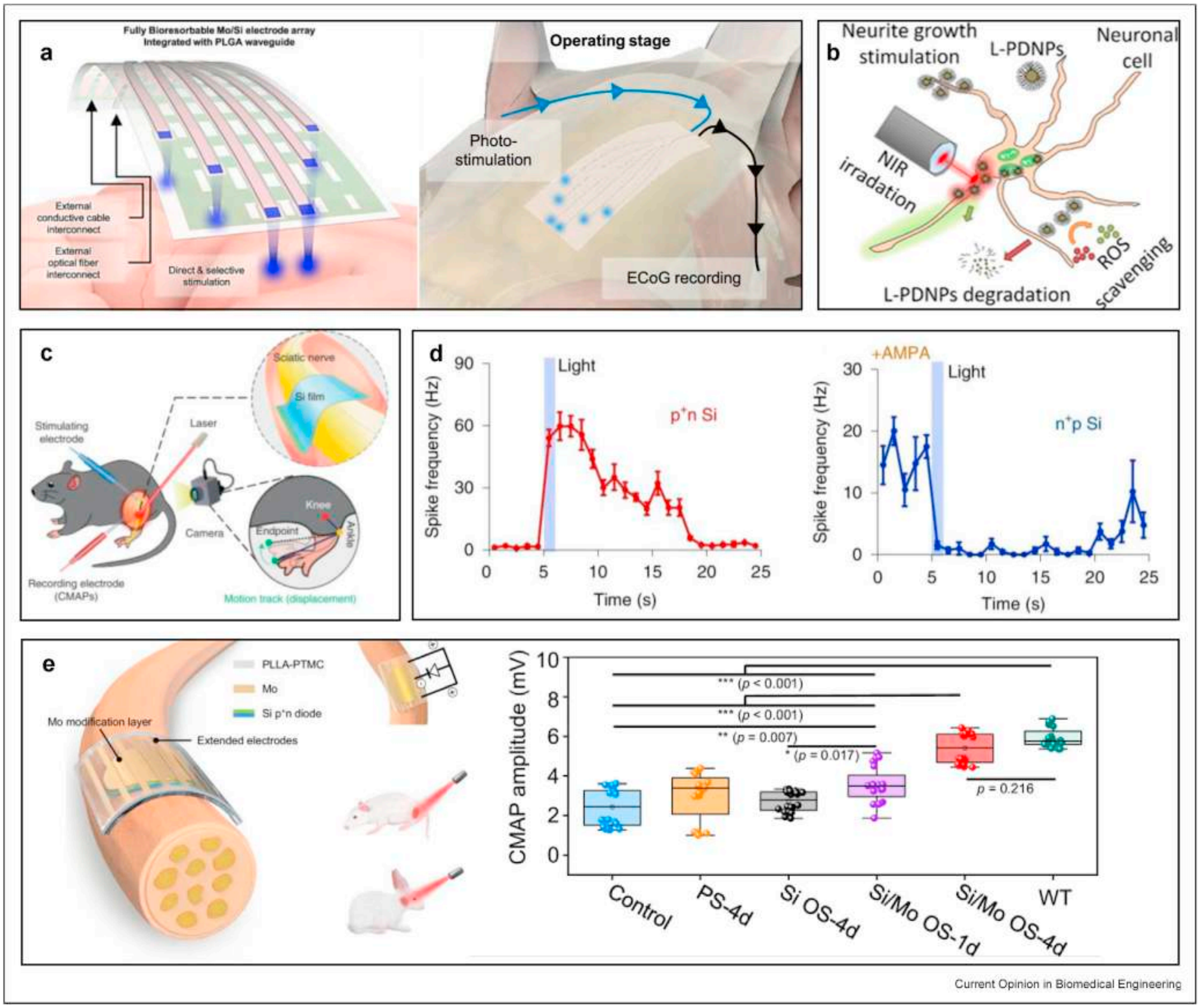
Optical neural interface represents a promising wireless and minimally invasive method to modulate neural activity. Myeongki Cho et al. designed a bioresorbable optoelectronic system capable of both electrophysiological recording and optical stimulation (Figure 2a) [19]. PLGA is adopted to build the biodegradable polymer waveguide to allow optogenetic stimulation on selective regions. Together with biodegradation electrodes made of single crystalline Si and Mo thin films, the device enables precise optical stimulation and continuous interrogation of neural activities, offering an important tool for diagnosing neurological disorders. Moreover, Matteo Battaglini et al. developed lipid-coated polydopamine nanoparticles (L-PDNPs) for photothermal neural activation upon NIR radiation (Figure 2b) [20]. L-PDNPs were also found to suppress the accumulation of reactive oxygen species (ROS) and promote neurite outgrowth, demonstrating potential applications in tuning cellular behavior.

Furthermore, Yunxiang Huang et al. reported a nongenetic and remote optoelectronic device for neural modulation based on bioresorbable thin-film Si pn diodes (Figure 2c) [21]. The Si device was fabricated on a flexible polyethylene terephthalate (PET) substrate and the interface was decorated with a layer of gold nanoparticles to facilitate charge injection. Interestingly, the device is capable of both activation and inhibition of neural activity on sciatic nerves and the brain (Figure 2d), by producing polarity-dependent positive or negative photovoltages at the interface. Additionally, Pengcheng Sun et al. developed a biodegradable, flexible, miniaturized device intended for transdermal optoelectronic stimulation to modulate neural activity and promote nerve regeneration [22]. The device was based on thin film silicon pn diodes modified with a thin Mo layer on a poly (L-lactic acid) and poly (trimethylene carbonate) (PLLA-PTMC) substrate, integrated with an array of extended Mo electrodes to achieve a tripolar configuration (Figure 2e). The inclusion of the Mo modification enhanced charge injection and the effectiveness of neural stimulation. With the implantation of the biodegradable neural interface, transdermal photostimulation was applied to injured facial nerves in New Zealand rabbits, and the compound muscle action potentials (CMAPs) amplitude after 8 weeks closely approached that of the normal (wild-type) side, surpassing the results of other groups significantly (Figure 2e). This optoelectronic device retains ∼30 % of its initial photovoltage performance after 6 days of implantation, suggesting promise for phototherapy for functional restoration of facial nerves.

Bioresorbable neural interfaces based on electrochemical reactions

Electrochemical systems enable self-powered neural interfaces to induce electric fields or generate signaling molecules to modulate neural activities. The generated electrical signals are beneficial for tissue regrowth and function restoration of injured nerves by accelerating Wallerian degeneration and upregulating regeneration-associated genes. An important factor for nerve regeneration is associated with the provision of favorable microenvironments for nerve repair. Acceleration of Wallerian degeneration by low-frequency electrical stimulations can effectively promote vascular and axonal growth at early stages of injury and regulate the neurotrophic secretions [23,24]. For example, Liu Wang et al. proposed a fully bioresorbable self-electrified device, integrating a magnesium-iron manganese alloy (Mg−FeMn) galvanic cell and a multilayer polymer nerve conduit comprising PLLA-PTMC and PCL biodegradable polymers, for sciatic nerve regeneration (Figure 3a) [25]. The average output circuit voltage decreased with the degradation of electrodes from 0.984 V on day 1 to 0.068 V on day 3. The device can provide both electrical cues and topological guidance and successfully enhance motor function recovery in rodents with sciatic nerve injuries. Similarly, Luhe Li et al. proposed a partially degradable zinc (Zn)-oxygen battery with high volumetric energy density (231.4 mWh cm^{-3}), which effectively promoted the regeneration of long-gap injured nerves [26]. Moreover, to extend the lifetime of a fully biodegradable primary battery, Xueying Huang et al. have developed a bioresorbable zinc (Zn)−Mo primary battery to promote axonal growth of DRG neurons and generate

Figure 2



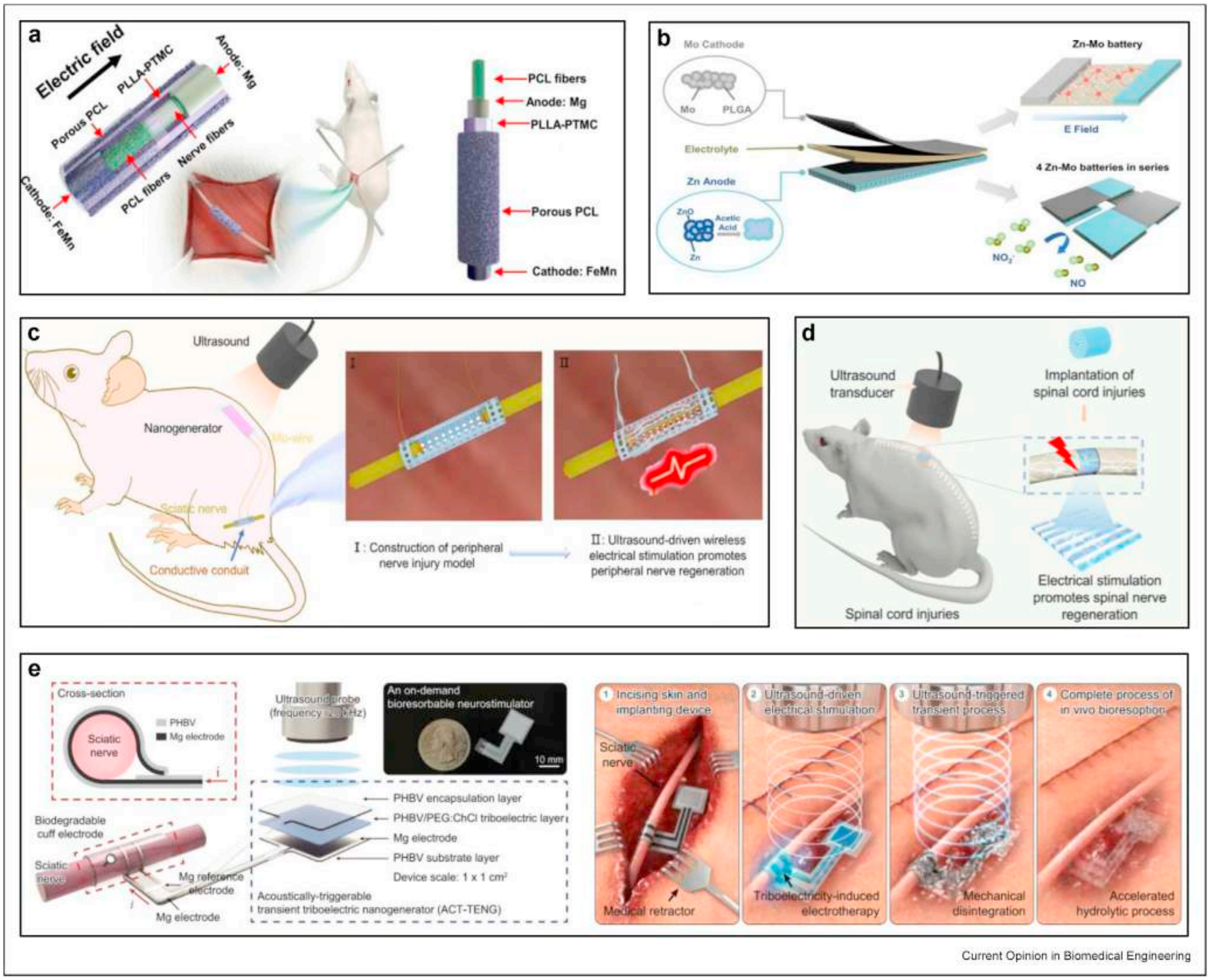
Bioresorbable optical interfaces. (**a**), A soft and flexible fully bioresorbable hybrid neural implant system constructed with a conductive Mo/Si bilayer ECoG electrode array stacked over a biodegradable PLGA waveguide. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License [19]. Copyright 2024, The Author(s). (**b**), An Organic and Biodegradable Multitasking Tool by Polydopamine Nanoparticles for Neuroprotection and Remote Neuronal Stimulation. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License [20]. Copyright 2020, American Chemical Society. (**c**), A bioresorbable Si diode implanted on the sciatic nerve to modulate the hindlimb movement. Reproduced with permission [21].Copyright 2022, The Author(s). (**d**), A bidirectional modulation thin-film Si diode structure mounted on the rat cortex to excite or inhibit neural activity [21].Copyright 2022, The Author(s). (**e**), A biodegradable transdermal optoelectronic stimulation neural interface. Reproduced with permission under the terms of the Creative Commons Attribution 4.0 International License [22].

gasotransmitters to modulate cellular behavior (Figure 3b) [27]. The battery comprised a cathode based on Mo particles, an anode based on sintered Zn particles, and a gelatin electrolyte. A prolonged operational time frame of up to ∼19 days was achieved. The arrangement of four Zn–Mo cells in a series promoted the voltage up to 2.3 V, enabling the generation of the gasotransmitter nitric oxide (NO) to modulate cellular activities.

Bioresorbable mechano-electric neural interfaces

Mechano-electrics neural interfaces convert mechanical vibrations into electrical signals and are often driven by ultrasound or body motivation through piezoelectric transducers or triboelectric nanogenerators (TENG) [28]. Ultrasonically powered bioresorbable devices feature advantages such as deeper penetration depth

Figure 3



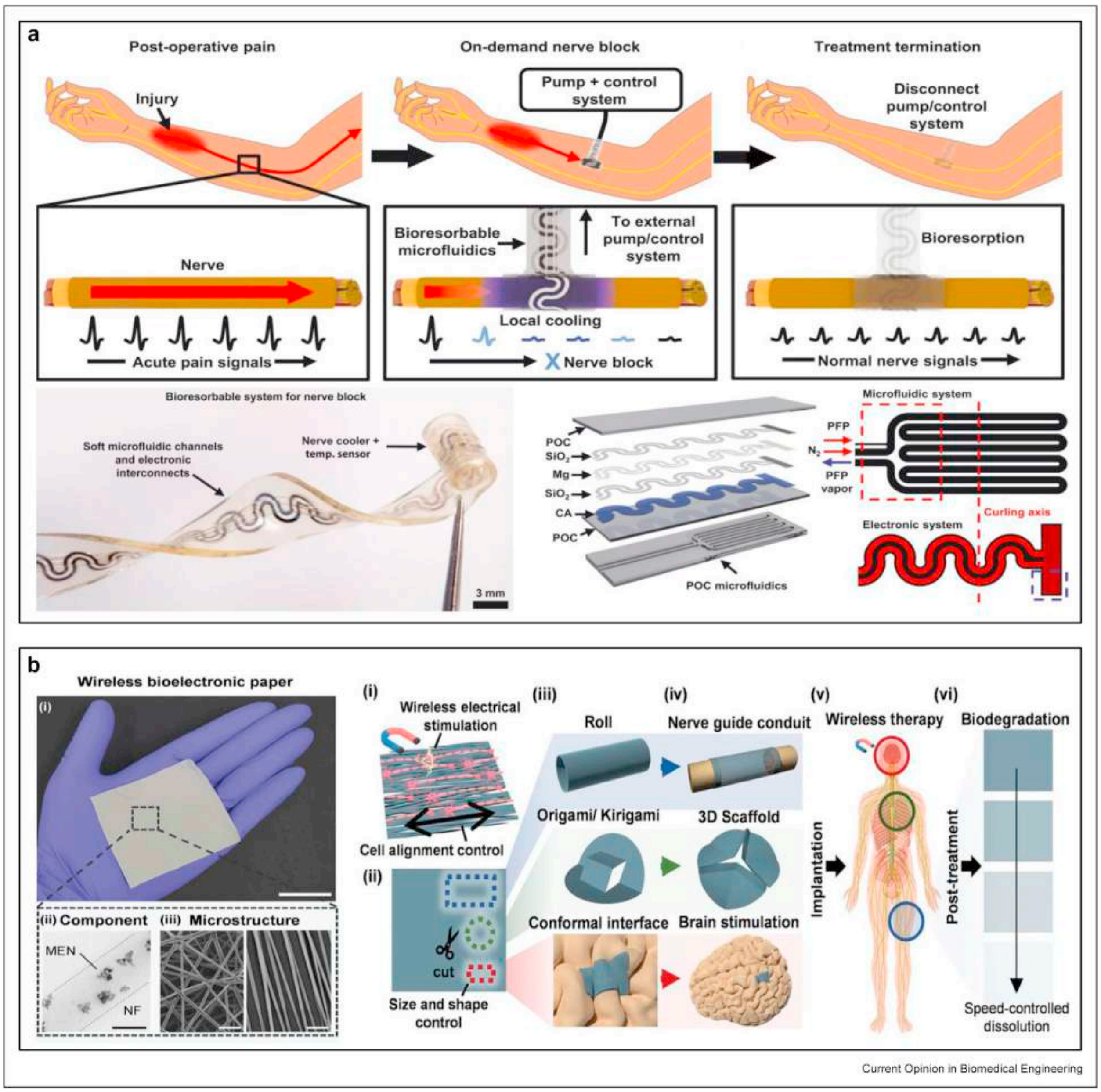
Bioresorbable electrochemical reaction-based and mechano-electric neural interfaces. (**a**), A fully bioresorbable self-powered electrochemical Mg−FeMn-based neural device for sciatic nerve regeneration. Reproduced with permission [25]. Copyright 2020, American Association for the Advancement of Science. (**b**), A fully bioresorbable Zn−Mo battery for modulating cellular behavior and for promoting axonal growth. Reproduced with permission [27]. Copyright 2023, American Chemical Society. (**c**), A Fully bioresorbable ultrasound-driven PHBV/PLLA/KNN-based piezoelectric nanogenerator for peripheral nerve regeneration via electrical stimulations. Reproduced with permission [29]. Copyright 2022, Elsevier. (**d**), A fully bioresorbable ultrasound-driven PLA/KNN/PDA-based 3D piezoelectric scaffold for nerve regeneration in the spinal cord. Reproduced with permission [30]. Copyright 2022, American Chemical Society. (**e**), A fully bioresorbable ultrasound-driven energy harvesting acoustically triggered triboelectric nanogenerator (ACT-TENG) for the treatment of peripheral neuropathy. Reproduced with permission under the Creative Commons Attribution 4.0 International License [31]. Copyright 2023, the Authors. Published by Springer Nature.

and device miniaturization. For example, Ping Wu et al. have reported a biodegradable piezoelectric nanogenerator (PENG) driven by ultrasound for tissue repair and function restoration of injured peripheral nerve (Figure 3c) [29]. The PENG consisted of biodegradable polymer including poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), poly (L-lactic acid) (PLLA), and potassium sodium niobate (KNN) nanowires, encapsulated by poly (lactic acid) (PLA) and PCL films. The device was implanted in the subdermal region and was connected to the biodegradable conductive nerve conduits (made of hydroxyethyl cellulose, soy protein isolate, and black phosphorus) through dissolvable Mo wires to accomplish ultrasound-driven electrical stimulation. Likewise, Ping Chen et al. proposed a degradable 3D piezoelectric scaffold based on PLA and KNN-modified polydopamine (PLA/KNN@PDA) to repair spinal cord injury (Figure 3d) [30].

Electrospinning of PLA and KNN@PDA yielded the piezoelectric scaffold, and motor function recovery was achieved with the proper dose of ultrasound radiation.

Moreover, Dong-Min Lee et al. proposed a fully bioresorbable acoustically triggered triboelectric nanogenerator (ACT-TENG) for the treatment of peripheral neuropathy (Figure 3e) [31]. The device was constructed with Mg electrodes, poly (3-hdroxybutyrate-co-3-hydroxyvalerate) (PHB) as the encapsulation layer, and PHB incorporating polyethylene glycol (PEG) and choline chloride (ChCl) as the triboelectric layer. The device can be eliminated on-demand using high-intensity ultrasound stimulation. The device provided high-frequency electrical pulses of 20 kHz and enabled effective therapy for compressional and hereditary peripheral nerve injuries. Interestingly, on-demand degradation of the device was achieved by high-intensity

Figure 4



Bioresorbable thermal and magnetoelectric neural interfaces. (**a**), A fully bioresorbable microfluid temperature control cooler for nerve blocking and acute pain management system. Reproduced with permission [32]. Copyright 2022, American Association for the Advancement of Science. (**b**), A magnetically driven flexible bioelectronic paper comprising biodegradable polymer fibers for wireless stimulation therapy. Reproduced with permission [34]. Copyright 2024, Wiley-VCH.

ultrasound (greater than 3.0 Wcm^{-2}) without inducing significant adverse effects.

Other bioresorbable interfaces (Magnetoelectric-based interfaces, cooling interfaces)

Apart from the aforementioned neural interfaces, other innovative bioresorbable devices have also been explored, such as thermal interfaces and magnetoelectric interfaces. For instance, Jonathan T, Reeder et al. have proposed a fully bioresorbable thermal interface consisting of a cooling microfluid channel and temperature sensing component for temporary pain management [32]. Figure 4a represents the implementation scheme of the bioresorbable thermal interface at the injured nerve. The device consisted of a temperature sensor and a microfluid system comprised of bioresorbable poly (octanediol citrate) (POC) elastomer with transcutaneous integrations to deliver liquid coolants (perfluoro pentane (PFP)) and dry nitrogen gas (N_2), achieving local cooling upon the evaporation of PFP in the channel. The device was capable of reversible nerve block by suppressing the conduction velocities and neural activity signals, thus possibly avoiding the negative effects of using opioid-related medications.

Furthermore, magnetoelectric interfaces offer another promising alternative for stimulating the neural system. They come with the benefits of deep tissue stimulation and miniaturization of devices. Certain millimetric battery-free magnetoelectric biocompatible implants are proposed for the endovascular stimulation of specific peripheral nerves hard to treat with traditional surgeries [33]. Recently, Jun Kyo Choe et al. developed a flexible and magnetically driven bioelectronic paper comprising biodegradable polymer fibers for wireless stimulation therapy (Figure 4b) [34]. The reported magnetoelectric nanoparticles (MENs) consisted of lead-free magnetoelectric cores of coupled $CoFe_2O_4$ (CFO) and piezoelectric shells of barium titanate ($BaTiO_3$ or BTO). These MENs were homogeneously aligned on degradable PLGA fibers via electrospinning to achieve the magnetoelectric paper. The device successfully achieved wireless stimulation of PC12 cells and showed the ability to create different 3D mesostructures through cutting or folding, offering a new avenue for remote neural modulation.

Conclusions

This review offers insights into recent advancements in bioresorbable interfaces for biomedicine including modulating neural activities and promoting function restoration following nerve injuries. Strategies include electrical, optical, electrochemical, mechano-electric, thermal, and magnetoelectric approaches. Liu Wang et al. have discussed the state-of-art applications of electrical neuromodulation and multimodal wireless neuromodulation techniques [28]. These interfaces serve as an effective alternative to traditional nonbiodegradable implantable electronics, aiming to eliminate the need for retrieval surgeries and mitigate long-term immune responses. Material strategies to achieve a controllable operational lifespan of the bioresorbable interfaces matching the therapeutic timeline are the key to maximizing clinical outcomes. The incorporation of stimuli-responsive components might provide one possible route. A precise on-demand biodegradable process can be achieved through systematic stimulus arrangements using sequence-based external triggering [35]. In addition, the exploration of multimodal stimulation can complement the advantages of each individual mode and enable customized, effective, and minimally invasive therapy. The incorporation of sensing components is also essential to enable closed-loop electronic platforms. Ankan Dutta et al. have reviewed electrical stimulation therapy systems for therapeutic systems, bioresorbable sensors for medical diagnostics, and closed-loop controller-enabled electronics, demonstrating the pathway of transient electronics toward connected biomedical applications [36]. Other research opportunities may revolve around integrating, processing, and fabricating components of bioresorbable devices, with an emphasis on combining novel materials with established ones without compromising system functionality. This pursuit should also prioritize achieving miniaturization while maintaining high-efficiency device output. Photolithographic patterning is the widely used method for fabricating high-resolution arrays on a flat surface [37]. Additionally, 3D neural interfaces that can conform to biological tissues also represent a significant trend in further development [38]. These interfaces can be fabricated using techniques such as 3D printing, self-folding, and self-rolling assembly [39]. Collectively, innovation in bioresorbable interfaces can provide essential tools for modulating neurological disorders and facilitating regenerative medicine.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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