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Synergistic 3D bioprinting and electrical stimulation for advanced electroactive tissue regeneration

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Abstract

Severe tissue injuries often disrupt the body's endogenous electric fields, making spontaneous healing nearly impossible. Although exogenous electrical stimulation (ES) is an effective intervention, conventional rigid electrodes are mechanically and geometrically incompatible with soft, dynamic biological tissues. To address this problem, three-dimensional (3D) bioprinting with conductive bioinks has emerged as a transformative strategy to create biomimetic, electroactive scaffolds. This review explores how combining 3D-printed scaffolds with ES promotes complex tissue regeneration. We first analyze the core cellular mechanisms by which ES accelerates tissue repair (e.g., guiding cell migration, enhancing proliferation and directing differentiation). We then summarize the mainstream 3D printing techniques (extrusion-based, inkjet, laser-assisted, photocuring-based printing) and detail the development of conductive bioinks from basic polymers to advanced electroactive materials, including piezoelectric, triboelectric, magnetoelectric, bio-battery, and optoelectronic materials for wireless stimulation. This synergistic strategy has been widely used to repair various tissue defects, including skin, nerve, bone, muscle and cardiac tissue injuries, and shows considerable therapeutic promise. Finally, we discuss ongoing clinical hurdles and offer a practical roadmap toward programmable scaffolds and closed-loop systems. Overall, this field is rapidly shifting from passive structural support to active electrophysiological guidance, laying the foundation for next-generation smart tissues.

Keywords: 3D bioprinting; Electrical stimulation; Conductive bioinks; Electroactive scaffolds; Tissue regeneration; Bioelectronics

1. Introduction

Endogenous electric fields (EFs) generated by cells, tissues, and organs during physiological processes play a crucial role in maintaining homeostasis by modulating cellular behaviors.[1,2] Under normal conditions, injury-induced EFs act as vital cues, guiding cell behavior toward regeneration.[3,4] However, in severe pathological states such as volumetric defects, complete nerve transections, or chronic diabetic ulcers, the native EFs at the lesion site are often irreversibly disrupted, rendering spontaneous regeneration via self-regulation ineffective. Consequently, exogenous electrical stimulation (ES) has been developed to artificially reconstruct these lost electrophysiological gradients.[5–7] Although conventional electroceuticals have shown potential for accelerating tissue repair, their clinical translation remains constrained by the physicochemical incompatibility between rigid, planar electronic devices and soft, irregularly shaped biological tissues. This mismatch causes inefficient signal transmission, limited conformal contact, and potentially mechanical damage.[8] Therefore, a key challenge in tissue engineering is to construct a physical scaffold that can seamlessly integrate with native tissue architecture and perform as a functional interface for exogenous ES.

Three-dimensional (3D) bioprinting has emerged as a powerful tool to address this structural challenge. Through the precise, layer-by-layer deposition of bioinks, extrusion-, inkjet-, laser-assisted and photocuring-based printing technologies can replicate the multiscale structural features of native extracellular matrix (ECM), ranging from macroscopic geometry down to microscale porosity.[9,10] This capability effectively overcomes the mechanical mismatch between conventional rigid devices and soft tissues.[11] However, most 3D-printed bioscaffolds made of non-conductive polymers (e.g., gelatin, polylactic acid) are electrically inert and incapable of conducting or mediating exogenous ES.[12–14] Therefore, successfully combining 3D printing and ES depends on developing electrically active bioinks that provide both structural biomimicry and effective signal transmission.

The evolution of such conductive bioinks has been through several stages. Early efforts using intrinsic conductive polymers (e.g., polypyrrole [PPy], polyaniline) were limited by poor processability and biocompatibility.[15] Subsequently, conductive nanomaterials (e.g., carbon nanotubes, metal nanoparticles) were embedded into

biocompatible matrices to balance conductivity and cytocompatibility.[16,17] Further blending with natural or synthetic polymers yielded composite scaffolds capable of both efficient electrical signal transmission and ECM-mimetic niche support.[18,19] More recently, research focus has shifted from static conductive frameworks to wireless electroactive scaffolds based on self-powered piezoelectric and triboelectric effects, and has further extended to magnetoelectric, bio-battery, and optoelectronic systems.[20–22] These advanced materials harvest ambient energy (e.g., mechanical, magnetic, biochemical, or light) and convert it into localized electric fields, enabling on-demand ES without implanted electrodes or external power sources. This synergistic strategy of 3D printed electroactive bioscaffolds that conduct exogenous ES or generate endogenous ES can overcome the limits of insulating scaffolds and/or rigid electrotherapy devices, greatly boosting the potential for clinical translation.

In this review, we explore the state-of-the-art advances in the synergistic application of 3D printed electroactive scaffolds and exogenous ES for tissue regeneration. We first summarize five key mechanisms by which ES promotes regenerative processes at molecular and cellular levels: guiding migration, enhancing proliferation, directing differentiation, regulating apoptosis and promoting growth factor secretion. We then analyze the technological characteristics of four mainstream 3D printing modalities (inkjet, extrusion-based laser-assisted and photocuring-based) and review the development of conductive bioink design, from early conductive polymers and nanoparticle-doped composites to emerging electroactive materials. Next, we highlight recent applications of this synergistic approach in wound healing, as well as in the repair of nerve, bone, muscle and cardiac defects (Figure 1). Finally, we discuss current challenges, such as long-term biocompatibility, degradation kinetics matching, and ES protocol standardization, and offer a roadmap for these technologies from the lab to clinical use.

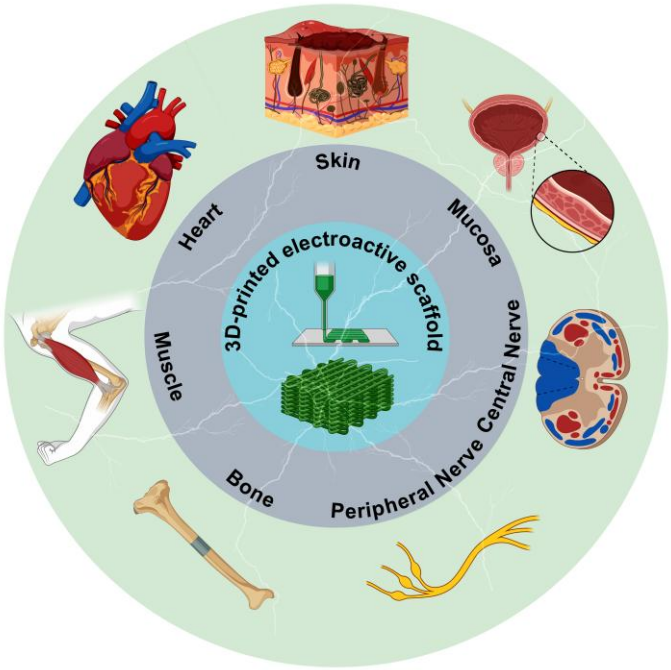

Figure 1. Schematic illustration of the holistic strategy combining 3D bioprinting and electrical stimulation for multi-tissue defect repair. Created in BioRender. Huang, J. (2026) https://BioRender.com/81amucy

2. The mechanism by which ES promotes tissue repair

Bioelectricity is a crucial factor in maintaining physiological homeostasis, ensuring the normal functioning of various organs through cellular regulation.[1] As a biophysical intervention, non-invasive ES has demonstrated considerable potential in tissue repair. By mimicking endogenous bioelectricity, it regulates a range of cellular behaviors, including migration, proliferation, differentiation, apoptosis, modulation of the inflammatory microenvironment, and secretion of growth factors,[8,23,24] thereby accelerating the tissue repair and remodeling processes. Building upon 3D-printed conductive and electroactive scaffolds, electrical stimulation synergistically promotes tissue repair through five primary mechanisms (Figure 2).

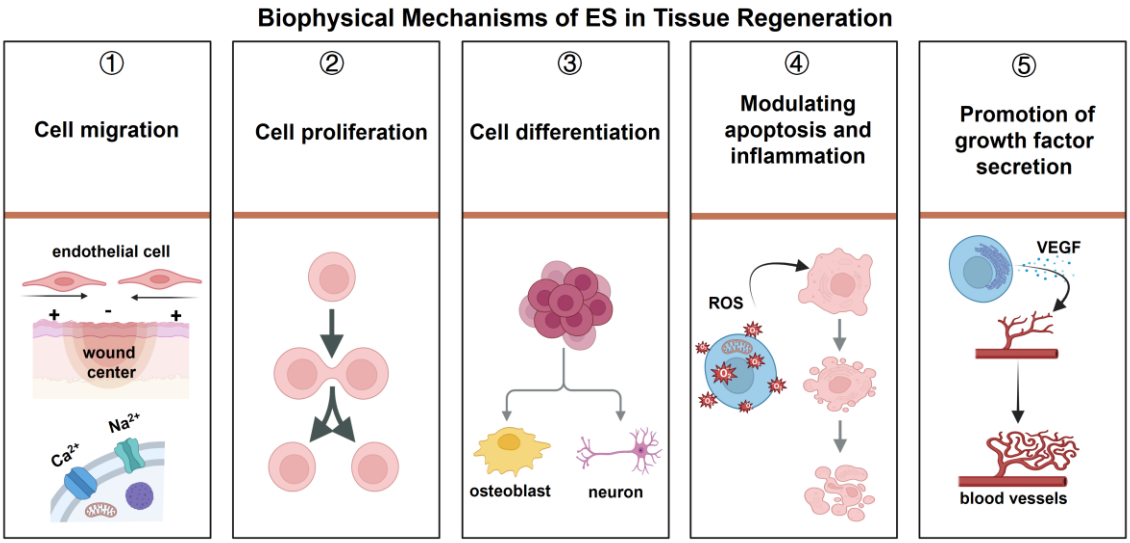

Figure 2. Schematic illustration of the biophysical and cellular mechanisms underlying electrical stimulation-mediated tissue regeneration. Created in BioRender. Huang, J. (2026) https://BioRender.com/u0arb3o

2.1 Cell migration

Electrotaxis refers to the directed migration of cells under an electric field and is a fundamental process in wound healing and endogenous tissue regeneration. Although the precise mechanisms driving this migration remain incompletely understood, studies indicate that it is governed by multiple factors. For instance, ES can activate specific receptors on the cell membrane (such as the epidermal growth factor receptor [EGFR], acetylcholine receptors, and integrins), thereby triggering downstream signal transduction cascades. Among these, MAPK-ERK1/2 and PI3K/Akt serve as the two core signaling pathways regulating electrotaxis.[25,26] EFs can induce the asymmetrical distribution of EGFR at the cell poles [27], activating PI3K to cause the accumulation of PIP3 on the membrane, which directs the rearrangement of cytoskeletal proteins and ultimately leads to directional cell migration. In addition to signaling pathways, EFs can also activate voltage-gated calcium (Ca^{2+}) and sodium (Na^{+}) channels, increasing cellular ion influx to further modulate cytoskeletal polarization and motility.[28,29]

2.2 Cell proliferation

Researchers have demonstrated that ES can promote the proliferation of various cell types, including fibroblasts, myocytes, and hair follicle cells, among others.[8] EFs exert

regulatory effects on multiple stages of the cell cycle, primarily involving gene transcription and translation. At the transcriptional level, EFs can modulate gene expression via pathways such as nuclear factor-kappa B (NF-κB), thereby accelerating cell proliferation.[30,31] At the translational level, ES modulates the activity of specific metabolic enzymes, thereby enhancing ribosome-mediated protein synthesis and expediting cell proliferation.[32] Furthermore, low-intensity ES enhances cellular proliferation by increasing PCNA expression and stimulating signaling pathways involved in cell cycle progression.[24]

2.3 Cell differentiation

In tissue engineering, ES can direct stem cell differentiation via complex intracellular signal transduction, the redistribution of cell membrane receptors, and alterations in transmembrane potentials.[33] Electric field-induced membrane depolarization triggers the opening of voltage-gated Ca^{2+} channels, leading to intracellular Ca^{2+} influx and subsequent regulation of Ca^{2+} signaling and energy metabolism between the endoplasmic reticulum and mitochondria. These events activate the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) pathway, a key regulator of cell fate determination and lineage-specific differentiation.[34,35] Studies have demonstrated that ES with specific parameters can upregulate the expression of osteogenesis-related genes (e.g., type I collagen, type II collagen, and Runx2) and enhance Ca^{2+} deposition within the ECM, thereby inducing the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs).[36] Similarly, ES can promote the differentiation of neural stem cells (NSCs) into functional neurons and facilitate neurite outgrowth.[33]

2.4 Regulation of apoptosis and the inflammatory environment

ES exhibits a dual regulatory capacity for maintaining microenvironmental homeostasis and clearing abnormal tissues. In the early stages of tissue repair, EFs can alter cell membrane permeability, leading to Ca^{2+} influx and inducing the generation of reactive oxygen species (ROS) within mitochondria. This process influences Bcl-2 family proteins (which regulate the balance between pro- and anti-apoptotic proteins) or modulates death receptor pathways on the cell membrane, thereby facilitating the clearance of inflammatory cells. [37,38] This helps to mitigate excessive inflammatory responses in tissues, establishing a favorable condition for subsequent healing. Conversely, in electro-sensitive tissues such as nerves and muscles, ES can activate the PI3K-Akt signaling pathway, exerting

pronounced anti-apoptotic and cytoprotective effects.[25] Furthermore, specific patterns of EFs can drive the polarized rearrangement of pro-repair receptors on macrophage membranes while activating Ca^{2+} influx mediated by channels such as TRPM7. This directs the polarization of macrophages toward the M2 phenotype (a pro-tissue repair and vascularization phenotype), accelerating the transition of the tissue from the inflammatory phase to the proliferative phase.[39] In the later stages of inflammation, ES can also downregulate the expression of pro-inflammatory cytokines, such as IL-6 and TNF, and reduce the number of mast cells, thereby accelerating the resolution of inflammation and preventing wound chronicity.[40]

2.5 Promotion of growth factor secretion

ES can optimize intracellular energy metabolism (increasing ATP production), trigger endoplasmic reticulum stress responses, and induce the reorganization of Golgi structures, thereby enhancing cellular protein synthesis and exocytotic secretion.[34,41,42] Under the intervention of exogenous EFs, the nitric oxide synthase pathway is activated, stimulating local cells to upregulate the secretion of key molecules such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF-1, FGF-2), insulin-like growth factor, and brain-derived neurotrophic factor. The elevated level of angiogenic factors upregulates the expression of CXCR4 and CXCR2 receptors on the surface of endothelial cells, facilitating the assembly of nascent capillary networks that supply sufficient oxygen and nutrients to the defect region. Concurrently, the secretion of neurotrophic factors induces reinnervation within the damaged tissue, ensuring the survival and functional recovery of the regenerated tissue.[23,27,43,44]

Elucidating this pathway from physical signals to cellular responses and tissue remodeling marks a fundamental shift in tissue engineering. It moves from passive structural bridging to active electrophysiological orchestration. Yet most current studies treat electrical stimulation as a static or uniform input, overlooking the dynamic nature of endogenous electric fields during regeneration. The real challenge ahead is not simply building better conductive scaffolds, but creating intelligent systems that can adapt their electrical cues in space and time. Achieving this precise spatiotemporal matching will be key to translating smart bioelectronic scaffolds into clinical reality.

3. 3D bioprinting technologies

As a core cutting-edge technology in tissue engineering, 3D bioprinting offers a solution for fabricating functional tissue constructs to replace damaged or diseased tissues. This technology enables the high-precision and highly reproducible construction of complex 3D spatial structures, demonstrating significant potential for scalable production. To date, a multitude of 3D bioprinting technologies have been developed, each possessing distinct advantages and specific applications. However, the most extensively utilized and broadly applicable printing modalities primarily consist of four main categories: extrusion-based, inkjet-based, laser-assisted, and photocuring-based printing, as shown in Figure 3.

3.1 Extrusion-based printing

Extrusion-based bioprinting is currently the most widely utilized and established technology in tissue engineering. Its fundamental principle relies on pneumatic or mechanical driving forces, which can be broadly categorized into pneumatic, piston-driven, and screw-driven systems, as shown in Figure 3a. These mechanisms operate by extruding highly viscous bioinks from a syringe cartridge through a nozzle as continuous filaments. Subsequently, these filaments are deposited and solidified layer-by-layer along pre-designed 3D pathways.

In the construction of conductive scaffolds, extrusion-based bioprinting exhibits distinct advantages. Beyond its simple manufacturing technique, cost-effectiveness, and operational flexibility, it possesses the distinct capability to print bioinks characterized by high viscosity and non-Newtonian fluid behaviors (accommodating viscosities up to 6×10^7 mPa·s).[45] This makes it highly suited for processing high-solid-content hydrogel systems that incorporate high concentrations of conductive fillers (e.g., carbon nanotubes, graphene) or high-molecular-weight conductive polymers.[46] The incorporation of such high-concentration fillers is imperative for establishing interconnected conductive networks within the scaffolds, thereby ensuring the efficient transduction of electrical signals.

Nevertheless, conventional extrusion-based bioprinting faces inherent challenges in processing conductive bioinks. High concentrations of conductive nanofillers and heterogeneous hydrogel formulations are prone to aggregation within the narrow nozzle lumen, often resulting in nozzle clogging. This consequently induces flow rate fluctuations

and non-uniform material deposition. Second, the printing resolution of this technique is relatively low (typically >100 μm),[47] rendering it inadequate for the fabrication of high-precision 3D architectures. Furthermore, the intense shear and extensional stresses generated during the forced extrusion of highly viscous bioinks can inflict substantial mechanical damage on the encapsulated cells. Under this printing modality, cell viability typically ranges from 40% to 80%, with higher extrusion pressures consistently resulting in diminished cell survival rates.[48]

3.2 Inkjet-based printing

Inkjet bioprinting is a non-contact additive manufacturing technique based on microdroplet deposition. Depending on the physical mechanisms of droplet generation, this technology is primarily classified into continuous inkjet and drop-on-demand (DOD) inkjet. Continuous inkjet has not been widely adopted in bioprinting, mainly due to its instability and high susceptibility to contamination. In contrast, DOD technology has found extensive applications in biomedicine and tissue engineering. Based on its core actuation mechanisms, DOD inkjet is further subdivided into thermal and piezoelectric modalities (as shown in Figure 3b): thermal inkjet employs micro-resistors to rapidly heat the fluid within microseconds, generating vapor bubbles whose expansive pressure forcefully ejects the droplets; piezoelectric inkjet utilizes the mechanical deformation of piezoelectric ceramic elements driven by alternating electrical signals to generate instantaneous compressive stress. Both inkjet modalities are capable of ejecting low-viscosity bioinks at high speeds and micrometer-level precision onto a receiving substrate, where they subsequently spread, crosslink, and solidify.[45,49]

In addition to its low manufacturing costs and high operational efficiency, inkjet bioprinting provides excellent deposition precision and spatial resolution for electroactive scaffold construction. The technique allows patterned deposition of conductive bioinks onto substrates, using nozzle diameters as small as 18 μm.[50] Furthermore, piezoelectric inkjet printing can achieve high cell viability (>85%), and even possesses the ultra-high precision requisite to encapsulate a single cell within an individual microdroplet.[49]

However, inkjet printing is subject to stringent fluidic and rheological constraints when processing conductive bioinks. First, this technique imposes rigorous demands on the surface tension and viscosity of the bioinks, typically requiring a viscosity range of 1–

25 mPa·s.[51] Furthermore, when incorporating high concentrations of conductive nanofillers or high-density cell suspensions into low-viscosity bioinks, these suspended particles are highly susceptible to gravity-induced rapid sedimentation and microscopic agglomeration. Such irreversible agglomeration leads to severe nozzle clogging, thereby disrupting the continuity of the printing process and the uniformity of material deposition. Additionally, the localized heating inherent to thermal inkjet printing (typically reaching 200–300 °C), combined with the impact velocity of the droplets and subsequent material accumulation, can further compromise overall cell viability.[52,53]

3.3 Laser-assisted printing

Laser-assisted bioprinting is a high-precision, nozzle-free, and non-contact printing technology that utilizes high-energy laser pulses to drive material transfer. A typical setup comprises a focused laser beam, a donor ribbon coated with a light-absorbing sacrificial layer and the bioink, and a receiving substrate. Upon irradiation of the sacrificial layer by the laser pulse, localized and instantaneous vaporization occurs, generating a high-pressure vapor bubble, and the expansion of this bubble propels the bioink away from the donor film, as shown in Figure 3c.[54,55]

In the realm of electroactive tissue engineering, laser-assisted printing demonstrates three distinct advantages. First, its unique nozzle-free mechanism bypasses conventional rheological constraints, eliminating the clogging issues typically caused by conductive fillers. Second, the room-temperature working environment and zero-shear technology not only prevent shear damage during the extrusion process, but the ultra-short femtosecond pulses also enable printing with virtually no heat transfer, which preserves high cell viability in biological cell printing applications. Furthermore, this technology exhibits outstanding control over 3D spatial positioning and structural dimensions.[50,55,56] Recent studies have demonstrated that near-infrared laser-assisted printing can deposit ultra-fine microdroplets with diameters as small as 58 μm, reaching an ultimate resolution capable of encapsulating one to three cells per droplet. This capability holds significant clinical translational value for the construction of complex biological tissue models.[57]

Despite its advantages, this technology remains constrained by several challenges, including the high cost of laser systems, complex donor-layer fabrication, and the difficulty of constructing mechanically robust three-dimensional architectures along the Z-axis.

These limitations have restricted its scalability and clinical translation in electroactive tissue repair.

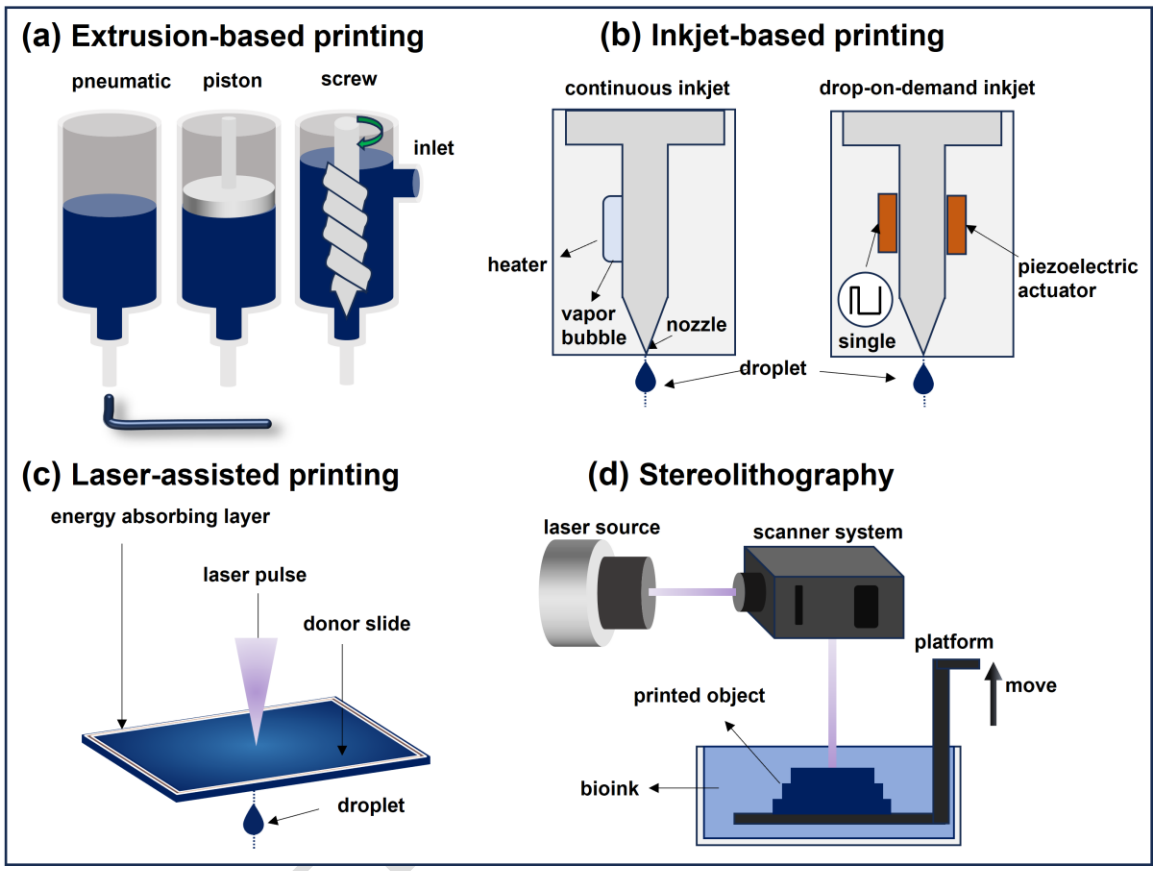

Figure 3. Schematic illustration of the four mainstream 3D bioprinting technologies. (a) Extrusion-based printing. (b) Inkjet printing. (c) Laser-assisted printing. (d) Stereolithography

3.4 Photocuring-based printing

Photocuring-based bioprinting represents a class of vat photopolymerization technologies driven by photo-initiated chemical crosslinking reactions. Its primary modalities include stereolithography (SLA), digital light processing (DLP), and two-photon polymerization (2PP). Distinct from extrusion-dependent physical processes, this technique utilizes specific wavelengths of light to irradiate liquid photosensitive bioinks containing photoinitiators. This triggers an instantaneous polymerization reaction under the light field, enabling layer-by-layer or continuous curing and shaping.[58]

Although these three technologies are all based on the principle of photopolymerization, they exhibit significant differences in their light modulation methods and fabrication characteristics. SLA employs a single tightly focused laser beam to perform point-by-point scanning crosslinking on the liquid surface. While it yields extremely smooth fabricated surfaces, its printing speed is limited by the cross-sectional area. DLP, on the other hand, utilizes a digital micromirror device to project a single-layer sliced image onto the liquid surface simultaneously, achieving instantaneous whole-layer curing via surface exposure. This area-independent, ultra-high fabrication efficiency significantly reduces the *in vitro* printing time for cells, making it highly favored for live-cell processing. In contrast, 2PP utilizes femtosecond lasers to induce non-linear optical effects, wherein polymerization only occurs at the focal point where photon energy is intensely concentrated. This unique mechanism allows it to surpass the traditional optical diffraction limit, enabling ultra-high-resolution printing at the sub-micron or even nanoscale level.[59–61]

In tissue repair strategies combining electrical stimulation, photocuring technologies possess unique advantages. They offer extremely high spatial resolution, capable of printing highly complex internal microstructures and anisotropic topographical morphologies with high fidelity. Notably, 2PP has achieved a resolution as low as approximately 100 nm.[62] Such precise microgrooves or oriented porous structures play a crucial role in guiding the directional extension of nerve axons and the polarized fusion of skeletal muscle cells. Simultaneously, the static crosslinking nature within the resin vat achieves a inherent zero-shear-stress condition, providing an optimal survival environment for fragile cells.[63,64]

Nevertheless, when applied to electroactive materials, this technology faces a significant challenge of optical shielding. Since the vast majority of highly conductive nanofillers are dark and opaque, they induce strong light scattering and absorption within the bioink. This leads to a precipitous drop in the light penetration depth, subsequently causing incomplete local curing or a loss of interlayer adhesion.[65] Therefore, balancing the optical transmittance of photosensitive bioinks with the density of the conductive network remains the core technical barrier currently facing photocuring-based conductive bioprinting.[66]

3.5 Emerging trends in 3D bioprinting technologies

Although the mainstream 3D bioprinting technologies discussed above have laid a solid foundation for electroactive tissue engineering, individual printing modalities often encounter specific limitations in practical applications. It is challenging to simultaneously balance high printing resolution, high cell viability, and the stringent rheological requirements for processing complex conductive bioinks. To overcome these inherent limitations, current bioprinting technologies are undergoing a profound iterative evolution, transitioning from singular to hybrid systems, and from macroscopic to micro/nanoscale dimensions.

Regarding the in-depth advancement of individual technologies, conventional extrusion-based printing has evolved to encompass advanced processes such as coaxial extrusion, microfluidic-assisted extrusion, and cryobioprinting. Coaxial extrusion, through the instantaneous fluidic shaping of core-shell structures, offers an optimal strategy for constructing biomimetic nerve guidance conduits and hollow vascular networks.[67,68] Microfluidic-assisted nozzles enable the microscale *in situ* rapid mixing of crosslinkers and conductive precursors, which substantially mitigates the agglomeration and clogging issues caused by high-concentration conductive particles, and possesses the potential to print asymmetric electrical Janus fibers.[69,70] Furthermore, cryobioprinting synergistically utilizes phase transition mechanisms to freeze and shape ultra-soft pure conductive polymers while endowing the scaffolds with highly interconnected hierarchical porous networks.[71–73] In the dimension of enhancing resolution, electric field-driven electrohydrodynamic (EHD) printing has broken the physical limits of traditional extrusion; its Taylor cone jet mechanism enables the sub-micron, ultra-high-precision deposition of highly viscous conductive bioinks.[74]

Moreover, to break through the bottlenecks of singular physical mechanisms, hybrid bioprinting—which deeply integrates printing modules with complementary advantages—has become a prominent trend. For instance, the extrusion-inkjet hybrid system effectively combines the advantages of extrusion-based technology in rapidly constructing large-volume load-bearing frameworks with the strengths of inkjet printing in localized high-resolution microdroplet patterning.[75] Meanwhile, the extrusion-photocuring hybrid strategy enables the synchronous fabrication of opaque conductive networks and high-precision insulating matrices.[76] These hybrid manufacturing paradigms achieve the

synergistic fabrication of macroscopic structural support and microscopic electrical/biological interfaces on the same platform, effectively overcoming the performance limitations of traditional single processes.[77]

Simultaneously, several disruptive emerging biofabrication technologies are reshaping the boundaries of electroactive tissue engineering. For example, Volumetric Bioprinting (VBP), acting as a layerless lithography technique, utilizes the principle of tomographic projection to generate complex centimeter-scale 3D physical entities in a rotating vat within tens of seconds. This not only thoroughly overcomes the major challenge of cell death caused by prolonged processing times in conventional layer-by-layer printing but also effectively prevents the gravity-induced sedimentation of high-density conductive fillers in low-viscosity bioinks.[78] On the other hand, acoustic-assisted bioprinting exhibits immense potential. Not only can it achieve completely nozzle-free droplet ejection via focused acoustic fields, fundamentally eliminating the risk of clogging by conductive particles; more crucially, by leveraging acoustic tweezers derived from standing wave fields, it can contactlessly guide the highly ordered alignment of internal conductive nanofillers or living cells prior to the crosslinking of the bioink. This provides a revolutionary physical intervention strategy for constructing skeletal muscle and central nervous tissues equipped with highly anisotropic conductive networks.[79]

In summary, the future fabrication of electroactive biomimetic scaffolds will move beyond traditional singular processes toward a next-generation intelligent manufacturing paradigm. This paradigm features multi-scale hybridization, multi-material integration, and the incorporation of novel acoustic, optical, and electrical modulations. Together, these advances will enable the reconstruction of the complex electromechanobiological microenvironments of native tissues with unprecedented fidelity.

4. Conductive and electroactive bioinks

Within this technological framework, the bioinks serve as the fundamental carrier for building tissue constructs. During the printing process or immediately following deposition, the bioink is stabilized and solidified via physical, chemical, or photocrosslinking, thereby precisely replicating the pre-designed macroscopic geometry and microscopic network architecture.[80] To ensure that the printed tissues and organs can perform normal

physiological functions, an ideal bioink must exhibit excellent rheological printability, mechanical strength comparable to that of the target tissue, and high biocompatibility.[81] Bioinks are typically formulated from hydrogel systems comprising natural biomacromolecules, synthetic polymers, or their blends. However, in regenerative strategies that incorporate the synergistic intervention of electrotherapy, conventional insulating biomacromolecules often fail to meet the functional requirements for electrical signal transduction. Consequently, developing electroactive bioinks capable of simultaneously providing structural support and electrical signal transduction has emerged as a pivotal step in advancing current 3D bioprinting technologies.[82–84] Currently, electroactive ink systems are mainly classified into passively powered conductive ink systems and self-powered ink systems.

4.1 Conductive bioinks

The performance of 3D-bioprinted electroactive constructs is highly dependent on bioink composition, which governs printing fidelity, electrical signal transduction, and the long-term viability of encapsulated cells.[83] The conductive bioinks developed to date are predominantly based on poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS), PPy, polyaniline (PANI), and their composites with other substances. Overall, they can be classified into three major categories: pure conductive polymer bioinks, conductive particle-loaded bioinks, and bioinks incorporating non-conductive polymers, as summarized in Table 1.

Table 1. Representative examples of polymer-based conductive bioinks, printing techniques, resolutions and conductivity.

Category	Composition	Technique	Resolution (μm)	Conductivity (S/cm)	Ref.
Pure conductive polymer inks	PEDOT:PSS/DMSO	DIW	30	28	[85]
	PEDOT:PSS/DBSA	DIW	20	0.1	[86]
	PANI/DBSA	DIW	250	20	[87]
	PANI/PPY/PSS	IJP	10	\	[88]

Composite inks with conductive fillers	PEDOT:PSS/Ag	APAP(DIW)	38	4.26×10^5	89
	PEDOT:PSS/CNTS	DIW	100	\	90
	PEDOT:PSS/MXene	DIW	200-500	15.258	91
	PEDOT:PSS/MXene	DIW	200	1600±400	92
	PPY/GA	DIW	210	\	93
	PANI/MXene	DIW	210	1650	94
Composite inks with non-conductive fillers	PEDOT:PSS/PEO	EHD	27.25±3.76	\	74
	PEDOT:PSS/GelMA	DIW	120	\	95
	PEDOT:PSS/GelMA	2PP	100	9×10^{-4}	96
	PEDOT:PSS/PEGDA	SLA	\	0.055	97
	PEDOT:PSS/PVA/PAA	DIW	60	0.0443	98
	PEDOT:PSS/PVAF	DIW	120	1.0653±0.2058	99
	PPY/GelMA/CS	DIW	160	797	100
	PPY/PLLA	DIW	260	7.5×10^{-5}	101
	PPY/HA	DIW	\	4.3×10^{-6}	102
	PANI/CNC	DIW	200	0.0335	103
	PANI/PEGDA	SLA	\	2×10^{-6}	104

4.1.1 Pure conductive polymer bioinks

Currently, pure conductive polymer bioinks are primarily based on three major types of polymers: PEDOT:PSS, PANI, and PPy. These materials possess highly π-conjugated electronic backbones, endowing them with high intrinsic electrical conductivity and electrochemical activity.[105] Owing to their intrinsic organic nature, pure conductive polymers facilitate efficient coupling between electronic charge carriers and ionic species in interstitial fluids during charge transfer, especially when compared to conventional inorganic metals.

PEDOT:PSS is highly favored in 3D bioprinting due to its excellent aqueous dispersibility and biocompatibility.[106] Yuk *et al.*[85] developed a high-performance PEDOT:PSS ink capable of being printed into microstructures with high resolution and

high aspect ratios. By employing a technique of lyophilization (freeze-drying) followed by solvent (water/DMSO) redispersion, the printed polymer networks could be converted into ultrasoft and highly conductive hydrogels. These were successfully applied in the fabrication of soft neural probes, enabling precise *in vivo* electrophysiological recording of single neurons. However, to induce phase separation, conventional PEDOT:PSS printing often requires harsh post-processing steps, such as lyophilization, the use of strong solvents (e.g., DMSO), or dry annealing. This restricts its potential for in situ biological applications. To overcome this barrier, Zhang *et al.*[86] utilized dodecylbenzenesulfonic acid (DBSA) to screen the electrostatic interactions between PEDOT and PSS, successfully inducing the physical crosslinking of exposed PEDOT chains via $\pi - \pi$ stacking at room temperature. They developed a fully injectable, self-healing soft PEDOT:PSS hydrogel, significantly broadening the application prospects of pure conductive hydrogels in minimally invasive biotherapies and *in situ* electrotherapeutic repair.

PANI is inherently difficult to process using additive manufacturing owing to its poor solubility and lack of thermoplasticity. To overcome these limitations, Menzel *et al.*[87] proposed a novel extrusion-based printing method leveraging a thermal doping process. They combined low-conductivity emeraldine base (PANI-EB) with DBSA; subsequent heating induced its transformation into highly conductive emeraldine salt (PANI-ES), simultaneously improving the rheological properties of the ink to suit extrusion processing, achieving a high conductivity of up to 20 S/cm.

Pure PPy frequently induces severe nozzle clogging due to its poor aqueous dispersibility and strong propensity for agglomeration. To achieve high-precision micro-patterning, Zea *et al.*[88] specifically engineered a composite conductive ink that integrates PANI and PPy with the polyelectrolyte sodium polystyrene sulfonate (PSS). The incorporation of PSS precisely tuned the surface tension and rheological properties of the PANI/PPy blend, thereby eliminating the nozzle clogging issue. Furthermore, it substantially enhanced the electrochemical stability of the resulting material.

4.1.2 Conductive bioinks incorporating conductive particles

Integrating conductive polymers with additional conductive fillers (e.g., Ag, CNTs, MXene, and graphene aerogel) can substantially enhance the overall electrical conductivity. These fillers typically possess abundant functional groups or surface charges, enabling self-

assembly with intrinsically conductive polymers (ICPs) via hydrogen bonding, π-π stacking, and electrostatic interactions of the bioink.

To enhance the electrical conductivity of PEDOT:PSS, Yang *et al.*[90] introduced CNTs into the bioink. Electrodes printed using this CNT-blended ink not only exhibited improved mechanical strength but also featured a dense CNT network that provided high-speed pathways for electron transport. Consequently, the areal capacitance of the electrodes reached 990 mF/cm², which is 2.33 times that of pure PEDOT:PSS. Liu *et al.*[91] incorporated hydrophilic two-dimensional (2D) Ti_3C_2 MXene nanosheets into PEDOT:PSS. The functional groups on the MXene surface established strong electrostatic and hydrogen-bonding interactions with PEDOT:PSS, yielding a printable bioink with an electrical conductivity as high as 1525.8 S/m.

2D carbon-based materials, such as graphene oxide (GO), are frequently utilized to improve the printability and porosity of conductive polymers, owing to their ultra-high specific surface area and mechanical strength. He *et al.*[93] designed a GO/PPy composite ink specifically tailored for direct ink writing (DIW) 3D printing. The incorporation of GO nanosheets not only endowed the PPy ink with excellent shear-thinning behavior and self-supporting extrusion capabilities but also, following printing, lyophilization, and chemical reduction, facilitated the successful construction of a graphene aerogel (GA)/PPy scaffold with a hierarchical porous structure.

Conventionally 3D-printed PANI electrodes typically suffer from low active material loading and poor charge transport. To address this challenge, Meng *et al.*[94] developed a highly concentrated MXene/PANI gel ink via a solvent-assisted self-assembly strategy. This molecular-level synergy between 2D and 0D materials effectively overcame the physical drawback of PANI's propensity for agglomeration. Furthermore, without the requirement of any insulating additives, it endowed the ink with superior shear-thinning and self-supporting properties, ultimately yielding a 3D-printed hierarchical porous gel network with an outstanding electrical conductivity of up to 1650 S/cm.

4.1.3 Composite conductive bioinks incorporating non-conductive polymers

Although pure conductive inks and bioinks loaded with conductive particles possess excellent electrical conductivity, their inherent rigidity and brittleness restrict their biomedical applications. To overcome these limitations, conductive materials are often

incorporated into non-conductive polymers, including gelatin methacryloyl (GelMA), poly(ethylene glycol) diacrylate (PEGDA), and poly(vinyl alcohol) (PVA), to form composite bioinks. Such formulations enhance printability, rheological behavior, and biocompatibility while maintaining adequate electrical conductivity.

For instance, to overcome the inherent instability of processing conductive polymers via electrohydrodynamic (EHD) printing, Chang and co-workers[74] introduced high-molecular-weight poly(ethylene oxide) (PEO) into PEDOT:PSS as a rheological modifier, which substantially elevated the viscosity and surface tension of the ink, thereby improving the printability of the PEDOT:PSS formulation. Zhang *et al.* [98] incorporated PVA and poly(acrylic acid) (PAA) into PEDOT:PSS. Leveraging the strong electrostatic interactions between PEDOT:PSS and the abundant free hydroxyl and carboxyl groups of PVA/PAA, they substantially increased the viscosity of the blended ink. Experimental testing demonstrated a shear adhesive strength exceeding 28.5 kPa on porcine skin surfaces.

In electroactive tissue engineering, biocompatibility is as important as electrical conductivity in bioink design. The incorporation of natural non-conductive polymers can provide a biomimetic extracellular matrix (ECM)-like microenvironment that supports the survival, proliferation, and function of encapsulated cells. For example, Serafin *et al.*[102] found that uniformly dispersing PPy nanoparticles (NPs) within gelatin and high-molecular-weight hyaluronic acid (HA) formed a biomimetic macromolecular network, effectively mitigating the inherent drawback of poor cell adhesion typically associated with pure PPy. While the introduction of insulating macromolecules inevitably leads to a decline in ink conductivity, Wan *et al.*[99] discovered a unique phenomenon when incorporating poly(vinyl alcohol-co-ethylene) (PVAF) into PEDOT:PSS. Beyond merely increasing the ink's viscosity and optimizing its shear properties, the abundant polar hydroxyl groups in PVAF acted as secondary dopants for PEDOT:PSS. This promoted the phase separation of PEDOT and PSS via the charge screening effect, thereby densifying the conductive network. Consequently, the composite ink achieved a high electrical conductivity exceeding 100 S/m, despite the presence of a substantial insulating matrix.

Furthermore, to meet the requirements of photocuring-based bioprinting, photo-crosslinkable non-conductive polymers are frequently integrated into pure conductive inks. For example, incorporating GelMA into PEDOT:PSS endows the ink with excellent

visible-light crosslinking capability (450–550 nm). Similarly, adding PEGDA to PEDOT:PSS or PANI enables photocurable 3D bioprinting, with subsequent UV post-curing stably raising the conversion rate of PEGDA to over 80%.[97,104]

In summary, within the realm of electroactive tissue engineering, there is no single material or process that is universally suitable for all clinical scenarios. For future practical applications, we must be guided by the physiological characteristics of the targeted tissues and rationally select the most compatible 3D printing modalities and conductive ink formulations tailored to specific clinical demands. Only through the integration of materials, architectures, and biological functions can optimal conductive scaffolds be successfully printed, thereby fully unleashing the potential of electrophysiological interventions in tissue therapy.

4.2 Electroactive bioinks

Electroactive bioinks represent a shift from passive charge conduction to active in situ power generation by incorporating energy-harvesting and conversion components into polymer or hydrogel matrices with suitable printing properties. Based on their underlying energy conversion mechanisms, this section highlights several representative electroactive bioink systems, including self-powered piezoelectric/triboelectric, magnetoelectric bioinks that harvest mechanical energy, as well as metabolically driven living bio-batteries and optoelectronic hybrid systems (Table 2).

Table 2. Representative examples of electroactive systems based bioinks, printing techniques, output voltage and power.

Category	Composition	Technique	Output voltage (V)	Output power (W/m^2)	Ref.
Piezoelectric systems	PVDF/SA/ZnO	DIW	\	\	107
	SMPU	DIW	340	\	108
	GelMA/$BaTiO_3$	DLP	0.02	\	109
	PCL/$BaTiO_3$	FFF	\	\	110
	PEMA/HA/$BaTiO_3$	DIW	\	\	111
	PLA/KNN	DIW	17.9	\	112

	SA/PAM/PHBV	SLA	0.4	\	[113]
Triboelectric systems	PVDF	FFF	260	690	[114]
	PDMS/PVDF/$FAPbI_3$	DIW	392	25870	[115]
	HEAA/PEGDA/SBMA	LCD	802	48.4	[116]
	ARO/AESO	DIW	22	0.34	[117]
	Mxene	DIW	\	0.8166	[118]
	PGS/PEDOT:PSS/NaCl	DIW	5	\	[119]
Magnetoelectric systems	PCL/$CoFe_2O_4$	DIW	\	\	[120]
	4-HBA/NCs	DLP	\	\	[121]
	GelMA/MENPs	2PP	\	\	[122]
Bio-battery systems	Alginate	DIW		13	[123]
	Alginate/GO/Bacterium	DIW	\	8.13	[124]
	CNC/Saccharomyces cerevisiae	DIW	0.6	12.54	[125]
Optoelectronic systems	PPY/GelMA/CS	DIW	160	797	[126]

4.2.1 Self-powered piezoelectric bioink systems

Piezoelectric materials contain spontaneously polarized electric dipoles that can intrinsically generate electrical signals upon experiencing mechanical deformation. Common piezoelectric materials include polyvinylidene fluoride (PVDF), barium titanate ($BaTiO_3$), and zinc oxide (ZnO). However, pure single-component materials are often difficult to utilize directly as bioinks for printing electroactive scaffolds; they typically require further optimization through modification or composite strategies.

PVDF is highly favored in flexible 3D printing due to its exceptionally high piezoelectric coefficient and outstanding flexibility. Liang *et al.*[107] developed a high-performance 3D-printable PVDF composite hydrogel ink capable of fabricating orthogonal grid dressings with vertically interconnected microporous structures. By employing sodium alginate (SA) for hydrophilic modification, the printed polymer network can be transformed into a highly absorbent and flexible piezoelectric scaffold, which was

successfully applied to promote scarless wound healing. To address the lack of continuous mechanical stimulation for piezoelectric scaffolds *in vivo*, Li *et al.*[108] proposed an innovative strategy that ingeniously couples the piezoelectric effect with the shape-memory effect. They integrated annealing-induced, high β-phase PVDF nanofibers with a 3D-printed shape-memory polyurethane (SMPU) framework to construct a smart bone repair scaffold with "two-stage *in situ* self-powering" capabilities. Triggered by body temperature, this scaffold undergoes shape deformation, thereby generating a micro-high-voltage electrostatic field.

$BaTiO_3$ is a classical ceramic piezoelectric material, often utilized in piezoelectric scaffolds due to its excellent piezoelectric properties and low toxicity. However, owing to its lack of thermoplasticity and high susceptibility to particle agglomeration, achieving high-precision cell-laden bio-additive manufacturing using traditional methods is extremely challenging. To overcome this limitation, Li *et al.*[109] proposed a novel photo-crosslinkable bioprinting method based on DLP. They combined polyethylene glycol (PEG)-surface-modified $BaTiO_3$ nanoparticles (PEG@BT) with GelMA. This surface coating effectively prevented the agglomeration of inorganic particles while concurrently improving the light transmittance and dispersibility of the ink, making it highly suitable for DLP processing. Meanwhile, Polley *et al.*[111] mixed $BaTiO_3$ with large-particle-size hydroxyapatite (HA) powder, ingeniously utilizing HA to improve the flowability of the ceramic powder on the print bed. Following high-temperature sintering and polarization, they obtained a biomimetic porous scaffold with a piezoelectric coefficient (approximately 3.08 pC/N) that perfectly matches the physiological properties of natural dry bone.

Driven by the requirements of *in vivo* applications, the development of biodegradable electroactive inks has emerged as a significant trend. Pure biodegradable piezoelectric polyesters, such as poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), due to their strong hydrophobicity, are highly incompatible with hydrogel matrices, which easily leads to phase separation and nozzle clogging. To achieve high-precision multi-layer printing, Huang *et al.*[113] specifically designed a unique ternary mixed solvent system integrating water, N,N-dimethylformamide, and dichloromethane. By optimizing the miscibility and rheology of hydrophobic PHBV and hydrophilic sodium alginate (SA)/polyacrylamide (PAM) networks, this solvent system eliminated printing phase separation and enabled the

fabrication of a piezoelectric gradient for dynamically adaptive tissue remodeling.

4.2.2 Self-powered triboelectric bioink systems

Unlike the piezoelectric effect, which depends on the crystal structure of materials, triboelectric nanogenerator (TENG) utilizes the coupling effect of contact electrification and electrostatic induction, enabling the efficient harvesting of energy from ultra-low-frequency biomechanical movements. Because their fundamental mechanism relies on differences in electron affinity, self-powered inks require the precise pairing of polar materials strictly according to the triboelectric series to facilitate effective charge transfer.

PVDF is frequently utilized as a classical tribo-negative matrix in 3D printing owing to its extraordinarily strong electron-withdrawing capability. However, pure PVDF often struggles to achieve a high content of electroactive phases during conventional printing and processing. Zain Karimy *et al.*[115] developed a high-performance PVDF composite ink capable of fabricating porous dielectric films. By employing DIW and introducing polymorphous perovskite nanofillers, they robustly induced the phase transition of PVDF from the non-polar α phase to the highly electroactive β phase, thereby significantly enhancing the material's triboelectric positivity and dielectric constant. Furthermore, Meena *et al.*[114] utilized the fused filament fabrication (FFF) process to naturally induce the polar crystalline phase of PVDF under elevated temperatures and shear forces. Simultaneously, by leveraging the microscopic surface roughness generated by the nozzle movement, they substantially increased the triboelectric contact area, achieving a hybrid enhancement of both piezoelectric and triboelectric effects.

Traditional TENG materials are highly susceptible to charge leakage and subsequent failure in high-humidity environments, such as body fluids. To overcome this environmental limitation, Zhuo *et al.*[116] presented a printable strategy that leverages ambient moisture to enhance output by integrating polar hydrophilic networks via liquid crystal display (LCD) 3D printing. They designed a superhydrophilic photo-curable resin ink by introducing zwitterionic species (SBMA) into a poly(N-hydroxyethyl acrylamide) (HEAA) polymer network. The polar functional groups of this ink can firmly trap free water molecules from the air and convert them into bound water, completely resolving the issue of charge leakage under high humidity and achieving a multifold leap in electrical output even at an extreme relative humidity of 90%.

For *in vivo* tissue engineering, traditional rigid triboelectric materials are highly prone to triggering inflammation, which restricts their application in *in vivo in situ* repair. To overcome this obstacle, Ma *et al.*[119] and Luo *et al.*[127] employed biodegradable poly(glycerol sebacate) (PGS) with a biomimetic modulus as a tribo-negative matrix and homogeneously incorporated highly conductive, tribo-positive PEDOT:PSS to develop a composite ink exhibiting shear-thinning characteristics. Combining 3D printing with particulate leaching techniques, they constructed a three-dimensional framework rich in hydrophobic micropores. When subjected to compression *in vivo*, the inner walls of these pores can undergo highly efficient contact-separation electrification. This architecture was successfully applied to accelerate endochondral ossification (ECO) repair and enable non-contact wireless electrical stimulation therapy.

4.2.3 Other emerging electroactive bioink systems

Beyond piezoelectric and triboelectric systems that rely on mechanical deformation, 3D-printed electroactive bioinks are expanding toward multi-physics field responsiveness and purely endogenous metabolism. In recent years, through meticulous material formulation and rheological design, researchers have ingeniously integrated magnetic nanoparticles, living microbial systems, and micro/nano solid-state devices into printable polymer matrices. This has led to the development of novel composite inks, including magnetoelectric, biological fuel cell, and optoelectronic heterogeneously integrated systems.

Incorporating inorganic magnetoelectric nanomaterials into polymer matrices is a crucial approach to achieving magnetically driven wireless power generation. Cobalt ferrite ($CoFe_2O_4$) is one of the most classical magnetoelectric materials; however, cobalt ions exhibit inherent heavy metal toxicity. To overcome this materials science obstacle, Kaviani *et al.*[120] specifically designed a magnetic nanocomposite ink with a core-shell architecture. Utilizing a sol-gel method, they coated a highly magnetically responsive $CoFe_2O_4$ core with a Mg_2SiO_4 silicate shell, subsequently melt-blending it with polycaprolactone (PCL). This endowed the printed composite network with excellent hydrophilicity and auto-buffered degradation capabilities, leading to its successful application in bone tissue regeneration strategies. Conversely, Fang *et al.*[121] selected carbon-based magnetized nanocookies (NCs) with a porous structure as the magnetoelectric material. They dispersed

the magnetoelectric particles in 4-hydroxybutyl acrylate (4-HBA) and leveraged the rapid localized crosslinking characteristics of DLP 3D printing to precisely expose the NCs at the photopolymerized edges on the gel surface. This "surface exposure" strategy completely eliminated the charge-shielding effect of the polymer network, enabling wireless magnetically induced microcurrents to stimulate cells at zero distance.

To achieve entirely endogenous, passive self-powering, living bio-battery inks that utilize microbial chemical metabolic energy for continuous power generation have emerged as a novel trend. The core design of such composite inks lies not only in maintaining cell viability but also in constructing an efficient metabolic symbiotic network and a cell-electrode electron transfer pathway. Regarding symbiotic metabolic power generation, Wang *et al.*[124] incorporated insulating graphene oxide (GO) into an alginate composite matrix and embedded bacteria. After printing and molding, these exoelectrogenic bacteria could not only continuously metabolize to generate electrons but also act as reducing agents to biologically reduce the GO *in situ* into highly conductive reduced graphene oxide. This living battery exhibited exceptional self-charging capabilities and a Coulombic efficiency of up to 99.5%, with its continuously generated metabolic microcurrents being successfully applied to drive *in vivo* neural electrical stimulation. For those seeking completely metal-free and environmentally biodegradable energy storage systems, Reyes *et al.*[125] formulated fungal battery inks for anodes and cathodes based on purely plant-derived cellulose. Driven solely by biochemical reactions, this 3D-printed fungal battery could generate a maximum power density of 12.54 $\mu W/cm^2$ per single cell and is fully biodegradable in the natural environment after disposal.

Traditional optoelectronic polymer inks typically rely on the chemical synthesis of complex organic conjugated molecules or inorganic semiconductors, which inevitably introduces issues like cytotoxicity and stringent processing conditions. Ershad *et al.*[126] abandoned the molecular-level optoelectronic modification of inks, proposing instead an optoelectronic heterogeneous integration bioink formulation strategy. By uniformly suspending micro-solar cells, fabricated via micro/nano processing, as micro-fillers directly into a GelMA matrix, they constructed a novel photoelectrically active bioink. The printed scaffolds' ability to instantaneously generate weak photocurrents under illumination provides a completely new paradigm for achieving non-invasive optically

controlled electrical stimulation, shifting the focus from chemical synthesis to the physical integration of microelectronic devices.

3D-printing bioinks are undergoing a profound evolution from single materials to multi-dimensional composites and cross-scale integration. Current research has successfully overcome traditional limitations in processing precision, polarization conditions, and biocompatibility through rheological tuning, phase-interface engineering, and process adaptation. This progress spans diverse energy systems, from piezoelectric and triboelectric platforms to magnetoelectric, bio-metabolic, and optoelectronic networks. Looking ahead, the development of smart bioinks that combine high energy efficiency, long-term stability in vivo, and complete biodegradability will remain a central focus.

5. Applications of 3D-printed conductive scaffolds in tissue engineering

3D-printed conductive scaffolds establish a unique physical interface for the profound integration of exogenous ES with the impaired tissue microenvironment. By leveraging their high-resolution customizability in spatial topology alongside superior electrochemical activity, these scaffolds precisely recapitulate the natural ECM. Consequently, they provide both a structural framework and an electrical signal transduction network to support ideal cell-matrix interactions. Facilitated by these bridging conductive networks, ES can modulate critical cellular behaviors, such as galvanotaxis, proliferation, and directed differentiation, which are central to accelerating tissue remodeling and regeneration. The integration of conductive or electroactive scaffolds with ES represents a powerful strategy for overcoming the limitations of conventional passive scaffolds and enhancing tissue regeneration. This chapter reviews recent advances in the application of this synergistic approach to wound healing, neural regeneration, bone repair, muscle and cardiac tissue reconstruction, emphasizing the underlying mechanisms and its potential to accelerate functional tissue restoration.

5.1 Wound repair

The mechanism of wound healing is a highly orchestrated cascade comprising hemostasis, inflammation, proliferation, and remodeling. During natural healing, an endogenous bioelectric field (approximately 10–60 mV) is generated at the wound margins to drive cellular migration toward the wound bed.[128] However, in instances of extensive

trauma, severe burns, or chronic diabetic ulcers, this endogenous electric field progressively attenuates or completely dissipates. This disruption results in delayed cell migration, disordered collagen deposition, and the formation of severe pathological scars.[129,130] Integrating 3D bioprinting technology with ES not only facilitates the precise reconstruction of the impaired electrophysiological microenvironment using conductive scaffolds but also guides tissue regeneration through customized macro- and micro-spatial architectures. Consequently, recent cutting-edge research has yielded breakthrough advancements in the realm of wound repair.[131,132]

5.1.1 Skin wounds

Skin wounds are one of the most common bodily injuries. While healthy individuals typically achieve spontaneous healing within a week, diabetic wounds are notoriously recalcitrant to self-healing. In these hard-to-heal diabetic wounds, bacterial eradication serves as a crucial prerequisite for successful wound closure. To achieve optimal bactericidal effects, Kumi *et al.*[133] integrated 3D bioprinting technology with intrinsically antimicrobial materials. As illustrated in Figure 4a, following 3D printing, the scaffold underwent *in situ* quaternization using glycidyltrimethylammonium chloride (GTMAC) to convert dibutyrylchitin (DBC) into quaternized chitosan (QCS), which was subsequently blended with PEDOT:PSS to fabricate a flexible 3D-printed electrode. Leveraging the abundant cationic groups on its polymer chains, this electrode directly adsorbed and ruptured negatively charged bacterial membranes via robust electrostatic interactions. Upon the superimposition of an external micro-pulsed electric field, the synergistic effect between this intrinsic electrostatic field and the applied electric field boosted the eradication rate of methicillin-resistant Staphylococcus aureus (MRSA) to over 98% in an *in vivo* diabetic infection model. This synergistic intervention attenuated the localized inflammatory response and propelled the wound toward epithelialized closure within 14 days.

Conventional exogenous electrotherapy relies heavily on external power sources, which severely restricts patient mobility. To address this, Liang *et al.*[107] fabricated a ZnO-modified PVDF/sodium alginate (ZPFSA) composite hydrogel using 3D bioprinting, harnessing the piezoelectric effects of ZnO and PVDF to deliver wireless ES. During the hemostasis and inflammation phases, the 3D-printed porous network rapidly absorbed

large volumes of wound exudate, undergoing significant vertical swelling; the resulting volumetric deformation stress stimulated the PVDF to generate piezoelectric microcurrents. Subsequently, in the proliferation and remodeling phases, as the wound formed an eschar and exudation diminished, the horizontal friction generated between the dressing and the skin due to daily human activities served equally well as a source of ES. By orchestrating a cascade of cellular migration, vascularization, collagen remodeling, and related growth factor expression throughout the healing process, this dynamic system substantially accelerated wound healing and prevented the formation of scar tissue within two weeks (Figure 4b).

High-quality wound regeneration relies not only on cellular proliferation but also on the highly ordered arrangement of the ECM. Lee *et al.*[134] utilized DLP technology to precisely engineer micro-topographies on the surface of conductive dressings to direct cellular behaviors. As depicted in Figure 4c, they employed a photosensitive, non-conductive polymer, GelMA, as the matrix, doped with the conductive polymer PEDOT:PSS. The incorporation of PEDOT:PSS not only endowed the hydrogel with excellent electrical conductivity but also substantially enhanced its mechanical tensile strength through electrostatic interactions between the PSS chains and the gelatin backbone. The conductive microgrooved scaffolds, coupled with ES, markedly activated the PI3K/AKT and MAPK/ERK signaling pathways in fibroblasts. This process significantly upregulated the secretion of fibroblast growth factors and collagen, thereby expediting wound repair.

ES devices and electrodes that directly contact the wound bed may increase the risk of infection and cause secondary tissue damage during removal. To circumvent this, Luo's research team developed a completely soft, biodegradable TENG based on PEDOT:PSS using 3D printing technology (Figure 4d). This device overcame conventional spatial contact limitations by utilizing limb movement to trigger the contact and separation of internal micropores. The resulting alternating spatial electric field could induce the formation of an electric double layer in the interstitial fluid at a distal distance of up to 44 mm from the wound. Remarkably, these nonadjacent wireless-induced microcurrents still managed to boost early-stage wound repair efficiency by over 336% and substantially promoted collagen deposition and angiogenesis.[127]

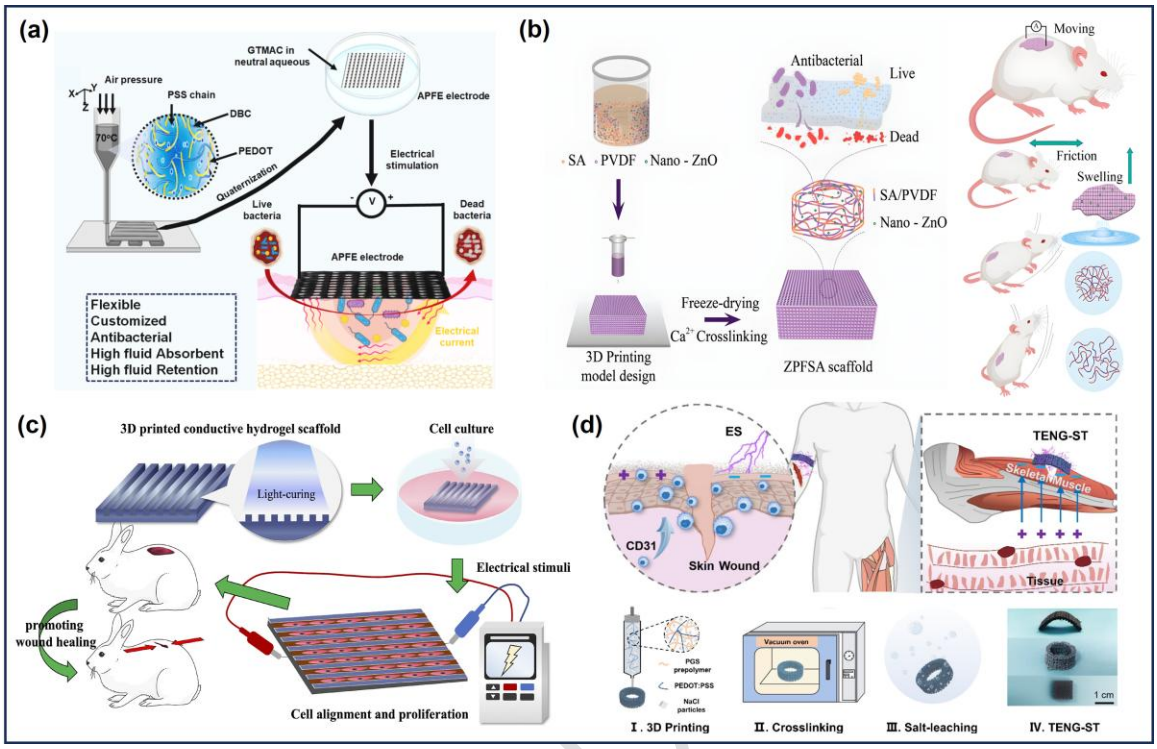

Figure 4. Applications of 3D-printed electroactive scaffolds synergized with electrical stimulation for skin wound healing. (a) Design and fabrication principles of the antimicrobial flexible electrode. The scaffold is extruded using a bioink composed of PEDOT:PSS and dibutyrylchitin. Modified and reprinted with permission from Kumi et al.[133] Copyright© 2025 Elsevier B.V. (b) The fabrication process and pro-healing mechanism of the 3D-printed piezoelectric hydrogel scaffold. Reprinted with permission from Ref.[107] Copyright© 2022, American Chemical Society. (c) A conductive hydrogel scaffold with microgrooved topography precisely engineered via DLP printing. Reprinted with permission from Ref.[134] Copyright© 2022 Elsevier B.V. (d) Schematic illustration of PEDOT:PSS-based 3D printing for tissue repair. Reprinted with permission from Ref.[127] Copyright© 2023, American Chemical Society

5.1.2 Mucosal wound

Wound repair of luminal mucosa confronts extreme microenvironmental challenges completely distinct from those of the epidermal surface, including continuous fluid flushing and high-frequency dynamic mechanical stretching. Conventional static,

insulating dressings frequently encounter adhesion failure or suboptimal histological remodeling in these regions, making the repair of internal mucosal wounds particularly challenging.

Nie *et al.*[135] developed a natural macromolecular composite formulation based on sodium alginate and hyaluronic acid, utilizing 3D bioprinting technology to construct a bilayered endometrial construct for treating endometrial injury. By depositing endometrial epithelial cells with high structural fidelity on the upper layer to reconstruct a dense mucosal barrier, and printing endometrial stromal cells within the underlying grid to induce vascularization, this strategy faithfully recapitulated the delicate hierarchical microenvironment of the endometrium. In a rat model of partial full-thickness uterine excision, the implantation of this 3D-printed bilayered endometrial construct demonstrated substantial regenerative advantages 90 days post-surgery. Figure 5a illustrates the conceptual model of this endometrial construct alongside a comparison of post-operative wound healing.

Oral ulcers represent a prevalent type of oral mucosal trauma. Targeting oral mucosal repair, Zhou and co-workers[136] developed a conductive polyacrylamide/sodium alginate crosslinked hydrogel composite containing reduced graphene oxide, as depicted in Figure 5b. Exhibiting inherent antibacterial, anti-inflammatory, and antioxidant properties, this composite acts as an electrical bridge that transforms the short circuit at the injury site into an intact circuit. This transformation effectively stimulates adjacent fibroblasts to secrete growth factors, thereby accelerating tissue regeneration. Evaluated in a rat model of full-thickness infected buccal mucosa defects, this hydrogel demonstrated exceptional anti-inflammatory and pro-healing efficacy, achieving rapid, scarless, and complete wound closure within seven days. This substantially enhances patient treatment comfort and compliance, providing a highly promising research avenue for oral mucosal repair.

For the mucosa of hollow organs with stringent fluid storage and anti-leakage requirements, simple hydrogels struggle to withstand tremendous dynamic tension. A recent strategy utilized a natural bladder acellular matrix featuring waterproof barrier and tensile properties as the substrate. A conductive micro-network of GelMA-chitin nanocrystals doped with 2D MXene nanosheets was subsequently 3D-bioprinted onto its surface, Figure 5c$_{I}$ shows the morphologies of the printed scaffolds at different doping

ratios. Under the stimulation of an optimized 400 mV alternating micro-electric field, the conductive network substantially provoked the paracrine potential (e.g., VEGF and nerve growth factor [NGF] secretion) of the loaded adipose-derived stem cells. This electromechanical synergistic intervention guided the dense regeneration of the detrusor muscle and the continuous reconstruction of the AE1/AE3-positive urothelial barrier. Concurrently, it induced the ingrowth of microvessels and nerve endings, achieving a bidirectional restoration of both the anti-leakage and autonomic contraction functions of the luminal mucosa, thus pioneering a novel pathway for bladder defect repair (Figure $5c_{II}$&$5c_{III}$).[137]

Current research on 3D printed electroactive scaffolds for wound repair mainly focuses on basic observations. Poor understanding of how electrical signals regulate cellular responses, coupled with the absence of standardized stimulation protocols for field strength, frequency, and timing, makes cross-study comparison difficult. Most designs target skin wounds and have not adequately addressed mucosal challenges such as fluid flushing, enzymatic degradation, and mechanical strain. Future priorities include elucidating molecular pathways, developing closed-loop adaptive systems, and rationally integrating antibacterial, conductive, topographical, and biodegradable functions.

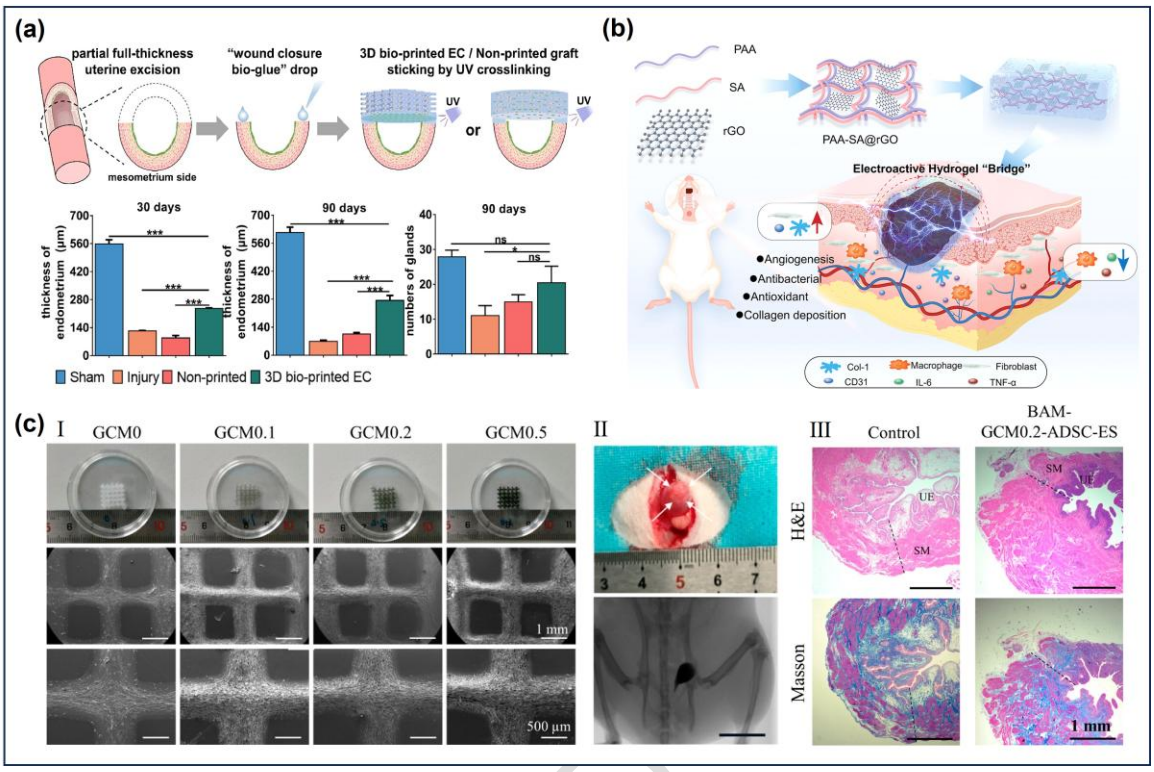

Figure 5. Applications of 3D-printed electroactive scaffolds synergized with electrical stimulation for mucosal tissue regeneration. (a) Schematic illustration of a 3D bio-printed bilayered endometrial construct for restoring injured endometrium and the comparison at 30 and 90 days post-operation. Reprinted with permission from Ref.[135] Copyright© 2023 Elsevier Ltd. (b) Schematic illustration of the synthesis of the PAA/SA/rGO-based conductive composite hydrogel and its mechanism for accelerating oral mucosal ulcer healing. Reprinted with permission from Ref.[136] Copyright© 2024 Wiley-VCH GmbH. (c) Systematic study of 3D-bioprinted decellularized matrix (DBM)-based conductive patches for bladder repair in rats. (I) Morphologies of the 3D-bioprinted conductive networks with varying MXene doping ratios. (II) Schematic of the bladder patch for morphological bladder repair. (III) Schematic diagram comparing the therapeutic outcomes of bladder tissue regeneration. Reprinted with permission from Ref.[137] Copyright © 2024, American Chemical Society.

5.2 Neural repair

The nervous system serves as the core information network responsible for maintaining somatic perception, motor functions, and homeostatic control. However,

neural tissue is highly vulnerable to irreversible damage caused by mechanical trauma, iatrogenic surgical injuries, and metabolic diseases. Central nervous system (CNS) injuries often result in the permanent loss of motor and sensory functions below the level of the lesion, accompanied by severe autonomic dysfunction.[138] Conversely, peripheral nervous system (PNS) injuries lead to sensory deficits or neuropathic pain.[139] Consequently, the high-quality reconstruction of neural pathways holds immense medical significance. In recent years, the therapeutic paradigm for nerve defects has gradually shifted from passive structural bridging methods, such as conventional direct suturing and autografting, toward cutting-edge strategies that integrate smart scaffolds with active physical interventions based on photoelectric, magnetoelectric, and piezoelectric effects.[140–143] Against this backdrop, the convergence of 3D bioprinting technology and ES paves a highly promising new avenue for the regenerative repair of complex nerve injuries.

5.2.1 CNS repair

In early explorations of remodeling the CNS microenvironment using conductive scaffolds, carbon-based nanomaterials demonstrated exceptional potential. Lee *et al.*[144] utilized SLA 3D printing technology to uniformly dope aminated multi-walled carbon nanotubes (MWCNTs) into a PEGDA hydrogel, thereby constructing a conductive neural scaffold with high-fidelity porous architectures. The Young's modulus of this composite scaffold reached 1.1 MPa, closely matching the elastic modulus of native spinal cord tissue, as shown in Figure 6a$_{I}$. Furthermore, its nano-topographical features promoted the adhesion and proliferation of NSCs. More importantly, upon the application of a 500 μA biphasic pulsed ES, the MWCNT conductive network amplified the transduction of electrophysiological signals, thereby activating the differentiation cascade of cells toward neurons and astrocytes, accelerating the growth of nerve cells (Figure 6a$_{II}$). This case study offered a highly promising research direction for CNS repair.

With the evolution of bioelectronic materials, 2D MXene nanosheets have been introduced to the forefront of CNS engineering owing to their exceptional hydrophilicity and high electrical conductivity. Yeh *et al.*[63] developed a novel conductive bioink based on methacryloyl silk fibroin, pectin, and soy phospholipid-modified MXene, achieving the first direct 3D bioprinting of NSC spheroids (Figure 6b). The incorporation of MXene-SP not only endowed the hydrogel with excellent shear-thinning properties and intrinsic

electrical conductivity but also moderately reduced its mechanical modulus, providing an ideal soft-matrix mechanical support for neurogenesis. Under a constant daily ES of 300 μA, this conductive network substantially promoted the proliferation and high-ratio neuronal differentiation of NSCs within the printed constructs. It was further validated to potently enhance synaptic vesicle cycling and synaptic transmission activity, thereby achieving a biomimetic reconstruction of the CNS micro-functional network.

Addressing highly complex CNS spinal cord injuries, precisely guiding neural axons to cross the lesion cavity and reconstructing conduction tracts remains a formidable challenge in this field. In 2024, Leahy *et al.*[145] utilized 3D bioprinting technology to precisely construct a PCL framework with pore dimensions highly tailored to the macroscopic anatomical geometry of human corticospinal tracts, and a conductive PPy coating was subsequently deposited onto its surface via *in situ* polymerization (Figure 6c). To further elevate the biomimetic dimension, the research team filled these large conductive microchannels with a neurotrophic ECM rich in collagen IV and fibronectin. When a continuous micro-electric field (200 mV/mm) was applied within these highly biomimetic 3D electromechanically coupled channels, neurons whose growth had previously stalled due to the hostile injury microenvironment gained a robust directional driving force for axonal extension, leading to a dramatic increase in the sprouting of long-distance neurites. This bioprinting strategy, combining glial-matrix support with dynamic, targeted electrophysiological stimulation, provides a blueprint for neural bridging following severe spinal cord injuries.

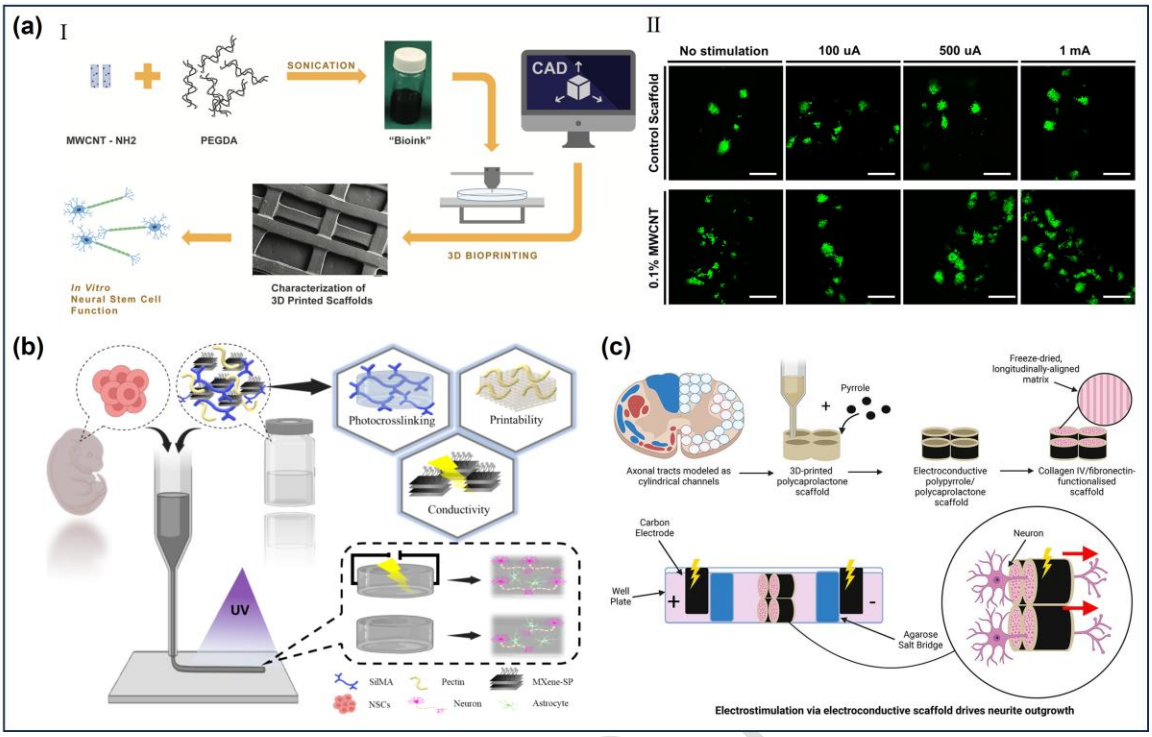

Figure 6. Applications of 3D-printed conductive scaffolds and bioinks synergized with electrical stimulation for central nervous tissue regeneration. (a) 3D-printed nano-conductive scaffolds based on multi-walled carbon nanotubes for nerve regeneration. (I) Schematic illustration of the fabrication process of 3D-printed conductive scaffolds. (II) Schematic diagram of the cell fluorescence comparison under various electrical stimulation parameters. Reprinted with permission from Ref.[144] Copyright© 2018 IOP Publishing Ltd. (b) Schematic illustration of the innovative MXene/SilMA-based conductive bioink for 3D bioprinting of neural stem cells. Modified and reprinted with permission from Yeh et al.[63] Copyright© 2025 American Chemical Society. (c) Schematic mechanism of a 3D-printed, biomimetic, neurotrophic, and electroconductive composite scaffold mediating spinal nerve repair via electrostimulation. Modified and reprinted with permission from Leahy et al.[145] Copyright© 2024 Elsevier Ltd.

5.2.2 PNS repair

The PNS is an essential conduit connecting the CNS to target organs, maintaining skeletal muscle contraction and sensory activity. Following severe trauma or long-gap defects, despite their intrinsic regenerative capacity, regenerating axons frequently lose

spatial directionality. This misdirection induces aberrant axonal coiling and neuroma formation, ultimately causing irreversible denervation-induced fibrosis and target organ atrophy. Consequently, the effective repair of peripheral nerves is of paramount importance for restoring physiological health and overall quality of life.

In neural tissue engineering, biomaterial scaffolds with high electrical conductivity and customized architectures are crucial for facilitating nerve regeneration. Poly(3,4-ethylenedioxythiophene) (PEDOT) is a frequently utilized conductive polymer in bioelectronic devices. However, the conventional 3D printing of PEDOT-based conductive scaffolds confronts challenges such as limited printing resolution, poor solubility, and the intrinsic brittleness of the material. Han *et al.*[146] developed a composite ink incorporating PEDOT nanoparticles into GelMA and chitosan. Utilizing DLP technology, they printed microgrooves that balanced ultra-high resolution with excellent electrical conductivity. *In vitro* experiments coupled with synergistic ES demonstrated that this scaffold promoted axonal elongation in PC12 cells. Furthermore, *in vivo* evaluations demonstrated the successful repair of a 10-mm rat sciatic nerve defect, comprehensively validating the efficacy of the GelMA/CS-PEDOT scaffold in treating peripheral nerve injuries (Figure 7a).

To highly recapitulate the complex composition and micro-electrical properties of the native peripheral nerve ECM, Cheng *et al.*[100] proposed a dual-bioink 3D printing strategy. By combining a conductive gelatin methacryloyl/chitosan/polypyrrole (GelMA/CS/PPy) foundational framework with a degradable gelatin ink loaded with neural cells, they successfully constructed a highly biomimetic double-network conductive scaffold, as illustrated in Figure 7b. Applying exogenous ES (300 mV/cm) within this customized electromechanical microenvironment remarkably upregulated the expression of core genes closely associated with neurogenesis (e.g., *GAP43*, *TUBB3*, *NGFR*, and *Nestin*). This drove the polarized differentiation of cells toward mature neurons and the formation of synaptic networks, providing a robust translational perspective for peripheral nerve regeneration.

For the *in vivo* application of conductive materials in repairing long-gap defects, the aligned topographical structure and suture-resistant mechanical toughness of the guidance conduit are equally indispensable. In 2020, Zhao's research team[147] ingeniously integrated SLA 3D printing with electrospinning technology to precisely fabricate a composite

conductive nerve guidance conduit (NGC). This NGC featured a polypyrrole/silk fibroin (PPy/SF) core and a flexible electrospun network shell. Upon seeding with Schwann cells and the application of a 100 mV/mm micro-electric field, this conductive framework potently stimulated the paracrine potential of the cells, markedly upregulating the secretion levels of core neurotrophic factors such as brain-derived neurotrophic factor, NT-4/5, and NGF. Evaluated in an *in vivo* 10-mm rat sciatic nerve defect model, this synergistic intervention, combining internal aligned conduction and external flexible wrapping with applied ES, promoted the robust bridging growth of axons and high-quality remyelination (Figure 7c).

Although conventional ES can effectively promote neural regeneration, the use of percutaneous leads poses risks of infection and secondary tissue injury. To overcome this limitation, Fang *et al.*[121] proposed an innovative strategy coupling 4D printing with magnetoelectric conversion. They developed a highly elastic polyurethane-based NGC, precisely exposing porous carbon-based nanocookies loaded with NGF on its surface, as illustrated in Figure 7d. This smart scaffold responds to non-invasive, high-frequency alternating magnetic fields, generating minuscule eddy currents to deliver direct wireless ES to the cells. More remarkably, the physical alterations triggered by the magnetic field, such as electrostatic repulsion, instantaneously increase the permeability of the nanopores, triggering the on-demand release of the internal NGF. This interventional strategy, which achieves precise spatiotemporal synchronization between a non-invasive physical micro-electric field and targeted biochemical factor delivery, substantially increased the myelin sheath thickness of newly formed nerve fibers. It provides a highly promising blueprint for combining wireless ES with bioprinting to facilitate neural repair.

Despite considerable progress, neural tissue engineering still faces several challenges. In CNS repair, precise axonal guidance across lesion sites and functional neural circuit reconstruction remain difficult. Most studies focus on short-term neuronal differentiation rather than long-term functional recovery. In PNS repair, effective regeneration across long-gap defects and prevention of neuroma formation are still major obstacles. In addition, wireless stimulation systems require further improvement in stability, energy efficiency, and biocompatibility. Future research should develop multifunctional scaffolds that integrate topographical, electrical, and biochemical cues. Precise spatiotemporal regulation,

combined with real-time monitoring, adaptive stimulation, and biodegradable materials, will be critical for successful clinical translation.

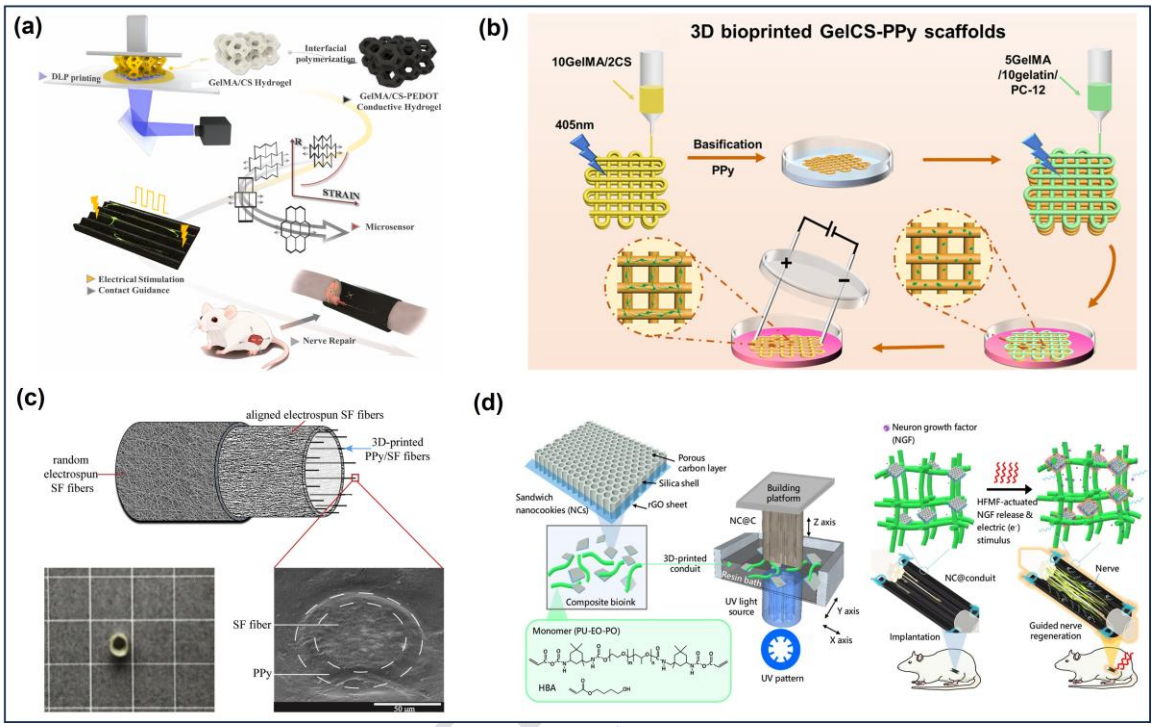

Figure 7. Applications of 3D-printed conductive scaffolds and advanced stimulation strategies in peripheral nervous tissue engineering. (a) Schematic illustration of the fabrication of the GelMA/CS-PEDOT-based bionic double-network conductive scaffold via DLP 3D printing. Reprinted with permission from Ref.[146] Copyright© 2024 Elsevier Ltd. (b) Schematic illustration of the preparation and electrical stimulation of 3D-printed GelCS-PPy conductive scaffolds. Reprinted with permission from Ref.[100] Copyright© 2025 Elsevier B.V. (c) Schematic illustration of the structure of the PPy/SF neural scaffold. Reprinted with permission from Ref.[147] Copyright© 2020 Elsevier Ltd. (d) Schematic illustration of the 4D-printed stretchable nerve conduit and the mechanism of magnetic-electric stimulation-mediated repair. Modified and reprinted with permission from Fang et al.[121] Copyright© 2020 Springer Nature.

5.3 Bone repair

Bone tissue inherently exhibits piezoelectric properties, generating an endogenous electrical potential that plays an irreplaceable stimulatory role in bone healing. However,

in cases of critical-sized bone defects, simple static physical scaffolds frequently suffer from central necrosis due to poor early-stage vascularization and adverse inflammatory responses. In recent years, 3D-printed electroactive scaffolds have provided a revolutionary engineering approach for reconstructing the electrophysiological microenvironment within bone defect regions by integrating conductive networks, *in situ* piezoelectric effects, and exogenous physical interventions.[148–150]

Among early interventional strategies in bone tissue engineering, introducing highly conductive nanomaterials to enhance charge transport efficiency represents a crucial method to accelerate bone repair. In 2021, Silva *et al.*[151] utilized extrusion-based 3D printing technology to uniformly dope MWCNTs into a PCL matrix, successfully constructing a highly biocompatible composite conductive bone scaffold. In an *in vivo* rat calvarial defect model, the synergistic effect of the MWCNT conductive network and applied ES promoted angiogenesis within the defect region. This provided an abundant blood and oxygen supply to support the Ca^{2+} phosphate mineralized deposition of the nascent bone matrix, ultimately inducing the formation of thicker, larger-volume, and higher-quality bone tissue (Figure 8a).

Although implantable biomaterials utilizing conductive components to mimic the electrophysiological properties of native tissues have been introduced into the field of bone regeneration, the incorporation of electret materials to deliver stable and sustained ES remains rarely explored. Zhang's research team[152] employed melt electrowriting technology to fabricate a ZnO/PCL composite scaffold featuring an *in situ* electret to investigate its efficacy in bone regeneration. Figure 8b illustrates the fabrication process of this scaffold and its underlying mechanisms for promoting bone tissue repair. The micro-electric field generated by this scaffold potently suppressed pro-inflammatory M1 macrophages and directed macrophage polarization toward the pro-healing M2 (anti-inflammatory) phenotype. These polarized M2 macrophages secreted high levels of anti-inflammatory cytokines and growth factors. This immune-driven paracrine effect subsequently orchestrated the osteogenic differentiation of BMSCs alongside the tube formation of vascular endothelial cells.

A major challenge in piezoelectric tissue engineering is providing sustained mechanical stimulation to activate piezoelectric scaffolds implanted in deep tissues, such

as the femur, where physiological loading is often insufficient. This limitation remains a key barrier to clinical translation. In 2025, Li *et al.*[109] proposed a wireless ES strategy based on low-intensity pulsed ultrasound (LIPUS)-piezoelectric coupling. Utilizing high-resolution DLP 3D bioprinting technology, they covalently encapsulated polyethylene glycol-modified barium titanate piezoelectric nanoparticles and live BMSCs within a GelMA hydrogel framework, achieving integrated cell-laden manufacturing, as shown in Figure 8c. This strategy leverages highly penetrative LIPUS as a non-invasive mechanical force source. When ultrasound waves propagate to the 3D-printed scaffold deep within the body, the generated acoustic stress can *in situ* trigger the polarization of the BT nanoparticles, thereby generating ES. In an *in vivo* deep rabbit femoral condyle defect model, this method elevated local bone mineral density and bone volume fraction, achieving high-quality trabecular reconstruction.

Beyond directly inducing intramembranous ossification, cutting-edge electromechanical tissue engineering has begun pivoting toward a repair strategy with higher biomimetic dimensions: endochondral ossification. In a recent study, Ma *et al.*[119] precisely constructed a 3D-printed TENG scaffold based on poly(glycerol sebacate) (PGS). This scaffold is capable of harvesting subtle biomechanical energy at the implantation site and converting it into an *in situ* pulsed micro-electric field. Figure 8d presents a schematic diagram of the scaffold's fabrication and its principles for promoting bone repair. Experimental findings revealed that the triboelectric charges generated by this scaffold could modulate transmembrane calcium ion influx, subsequently profoundly activating the PI3K/Akt signaling pathway and remodeling the actin cytoskeleton. This substantially accelerated the transdifferentiation of chondrocytes into osteoblasts. This method of endochondral ossification offers a novel approach to the repair of bone defects.

In summary, printed electroactive scaffolds are reshaping bone tissue engineering by integrating electrical, mechanical, and biological cues to guide tissue regeneration. Future advances will likely move beyond simple osteogenic stimulation toward precise regulation of bone-immune interactions, vascularized bone formation, and endochondral ossification. The combination of self-powered electrical systems, real-time biosensing, and closed-loop therapeutic regulation may enable dynamic adaptation to different healing stages. Such intelligent and multifunctional platforms hold great promise for the treatment of large and

complex bone defects.

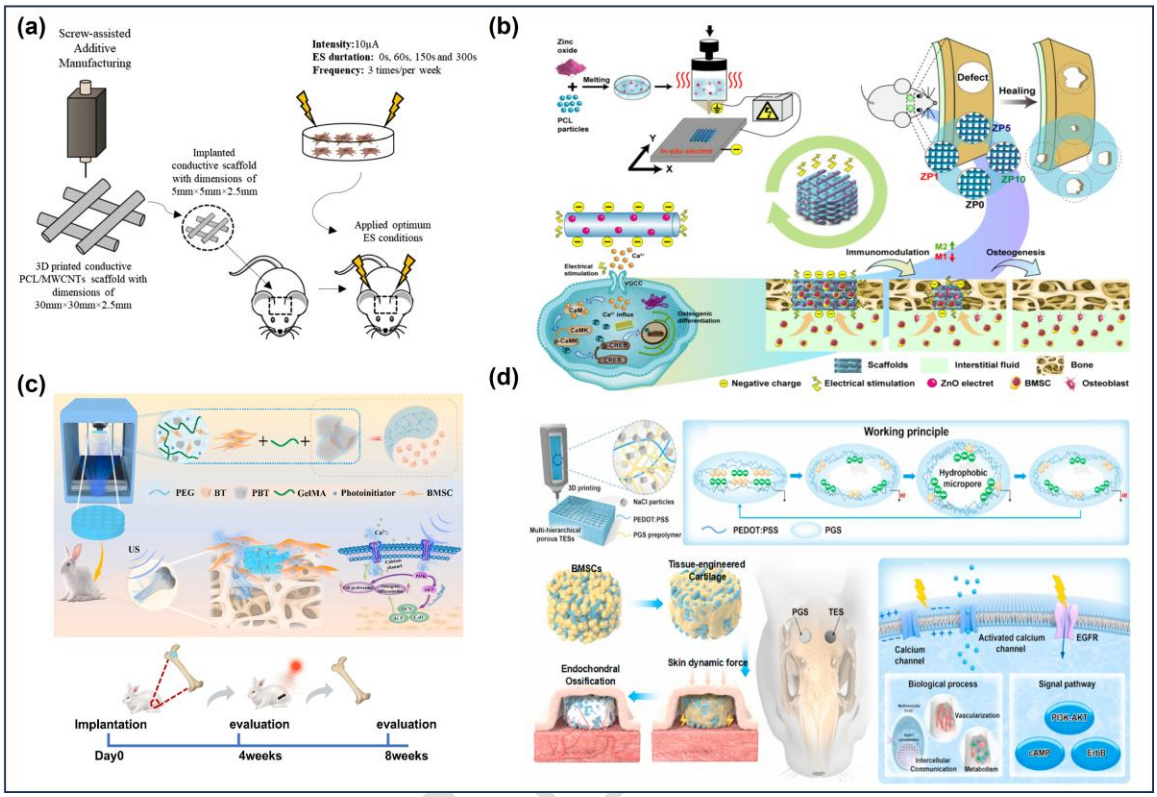

Figure 8. Applications of 3D-printed electroactive scaffolds and diversified electrical stimulation strategies in bone tissue engineering. (a) Schematic illustration of the PCL/MWCNTs-based 3D-printed conductive scaffold combined with exogenous electrical stimulation for bone tissue engineering. Modified and reprinted with permission from Silva et al.[151] Copyright© 2021 Springer Nature. (b) Schematic diagram illustrating the preparation of MEW-printed in-situ electret scaffolds with controllable electric fields and the underlying mechanism for enhancing bone defect regeneration. Reprinted with permission from Ref.[152] Copyright© 2024 Elsevier B.V. (c) Schematic diagram illustrating the fabrication process and therapeutic application of 3D-printed Gel/PBT@BMSCs hydrogel scaffolds. Modified and reprinted with permission from Li et al.[109] Copyright© 2025 Elsevier Ltd. (d) Design of BMSC-derived cartilage based-on TES for bone regeneration and schematic illustration of the mechanism in promoting bone tissue repair. Modified and reprinted with permission from Ma et al.[119] Copyright© 2026 Elsevier B.V.

5.4 Muscle tissue repair

Muscle is a highly organized and electroactive vital soft tissue. Although skeletal muscle can regenerate following minor injury, its endogenous repair capacity is often inadequate for severe damage such as volumetric muscle loss, leading to fibrosis and irreversible functional deficits. To overcome this limitation, the combination of 3D bioprinting and ES has emerged as a promising approach for muscle regeneration.[153]

In the exploration of constructing an electroactive muscle microenvironment, Wang *et al.*[46] utilized 3D bioprinting technology to develop conductive hydrogel scaffolds capable of enhancing myogenic differentiation. By uniformly integrating conductive PEDOT nanoparticles into GelMA, they not only endowed the bioink with excellent rheological and printability properties but also constructed a continuous conductive network within a three-dimensional space. This 3D-bioprinted conductive scaffold facilitated both intra- and extracellular electrical signal transduction. Various *in vitro* studies have demonstrated the efficacy of the highly conductive GelMA/PEDOT composite scaffold in promoting the proliferation, migration, and differentiation of C2C12 cells (Figure 9a).

The direct incorporation of conductive polymers into hydrogels is frequently hindered by the discontinuity of the resultant conductive networks and the susceptibility of these materials to rapid degradation within physiological fluids. To circumvent this limitation, Fortunato *et al.*[154] proposed a novel fabrication approach utilizing biocompatible gelatin as a flexible load-bearing substrate and a highly conductive PEDOT:PSS solution as a functional ink for precise deposition via inkjet printing. Experimentally, this device proved capable of delivering exogenous ES to the seeded muscle cells with high fidelity, driving their polar alignment and subsequent differentiation into mature myotubes (Figure 9b).

For volumetric muscle loss, the recapitulation of the parallel-aligned and densely packed myofibrillar architecture inherent in native muscle serves as the physical prerequisite for functional bridging. Bilge *et al.*[155] proposed an innovative strategy that balances structural anisotropy with eco-friendly synthesis: utilizing carbonaceous materials recovered from algal biomass and doping them with MWCNTs to endow the scaffold with excellent electrical conductivity. Leveraging 3D printing technology, this conductive ink was precisely patterned into scaffolds with a parallel-aligned topology, as depicted in

Figure 9c. This biomimetic design faithfully recapitulated the native muscle microenvironment. While providing electrophysiological signals, it regulated the polar extension of myocytes via physical contact guidance, demonstrating tremendous potential for muscle regeneration.

Beyond static conductive networks, dynamic bioelectrical cues driven by physiological mechanical forces offer a more biomimetically significant solution for skeletal muscle tissue engineering. In 2025, Sonaye *et al.*[156] developed a novel bioink possessing piezoelectric properties using natural bioactive materials such as sodium alginate, gelatin, and chitosan. Employing extrusion-based 3D bioprinting technology, they constructed a high-resolution composite scaffold with a mechanical modulus closely matching the stiffness of native muscle (Figure 9d). Crucially, when subjected to external mechanical forces, the scaffold's piezoelectric properties can *in situ* generate localized ES. The synergistic effect of this electromechanical conversion mechanism and excellent biocompatibility promoted the adhesion and differentiation of C2C12 muscle cells, providing an active regenerative therapeutic strategy for treating severe soft tissue trauma.

Overall, electroactive scaffolds have shown great promise for enhancing myogenesis and promoting functional muscle regeneration. However, muscle repair still struggles with recapitulating aligned myofibrillar architecture and preventing fibrosis after volumetric loss. Future research should move beyond enhancing myogenic differentiation toward the coordinated reconstruction of muscle fibers, vascular networks, and neuromuscular junctions. In addition, mechanoresponsive and self-powered bioelectronic materials may provide biomimetic stimulation that better matches the physiological demands of regenerating muscle. Such advanced multifunctional platforms are expected to improve muscle strength, contractile performance, and tissue integration.

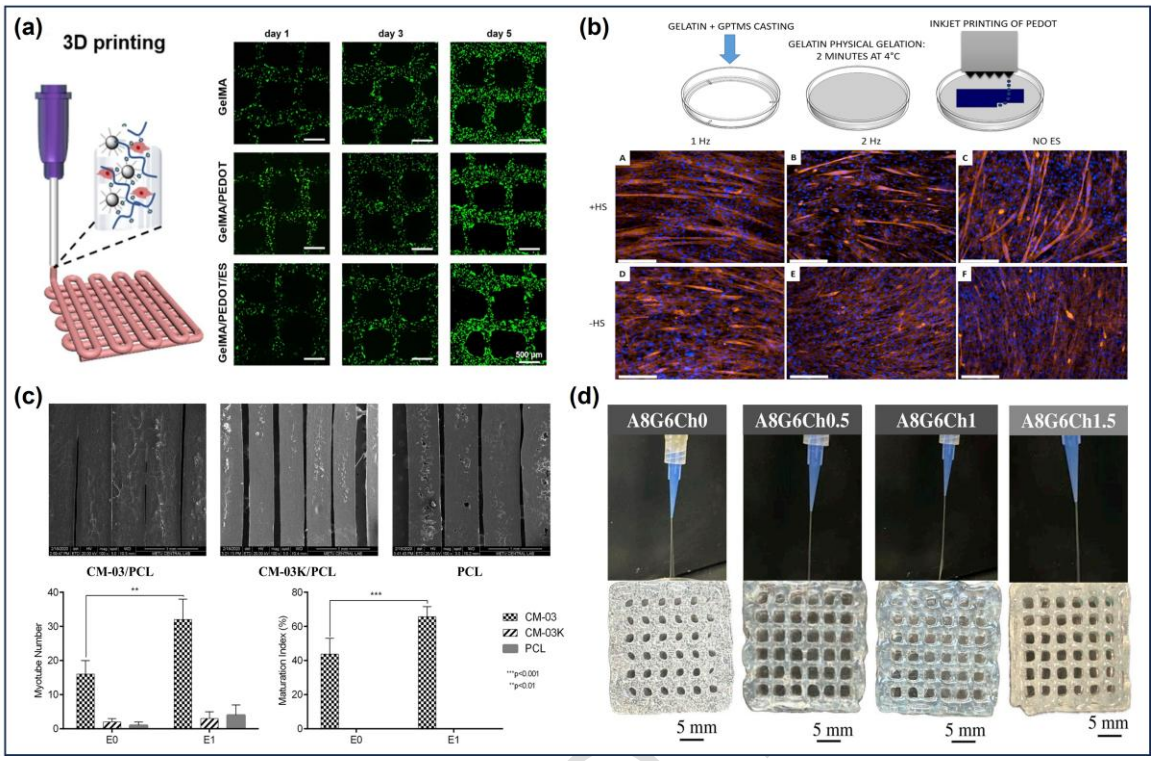

Figure 9. Applications of 3D-printed electroactive scaffolds and advanced manufacturing technologies in muscle tissue engineering. (a) Schematic illustration of the fabrication of 3D-bioprinted conductive hydrogel scaffolds for enhanced myogenic differentiation (Left). Live (green)/dead (red) staining of C2C12 cells in the GelMA/PEDOT hydrogel scaffolds after 1, 3 and 5 days (right). Modified and reprinted with permission from Wang et al.[46] Copyright © 2021 Oxford University Press. (b) Schematic illustration of inkjet printing of PEDOT on a cross-linked gelatin substrate (top). Comparison of DAPI (nuclei) and Phalloidin TRITC (cytoplasm) staining under 1 Hz, 2 Hz, and no electrical stimulation after 7 days (Bottom). Reprinted with permission from Ref.[154] Copyright© 2018 Elsevier B.V. (c) Schematic diagrams of different 3D-printed scaffold structures (top). Comparison of the number of myotubes and maturity index calculated from MHC staining (bottom). Modified and reprinted with permission from Bilge et al.[155] Copyright © 2021 Springer Nature. (d) Schematic diagram of printed scaffold structures using different bioink formulations. Reprinted with permission from Ref.[156] Copyright © 2025 Sage Publications.

5.5 Cardiac tissue repair

Ischemic myocardial injury, such as myocardial infarction, leads to irreversible

cardiomyocyte death and the formation of electrically insulating fibrotic scar tissue, which disrupts normal cardiac electrical conduction and synchronized contractile function, potentially resulting in cardiogenic shock and death. Given the limited regenerative capacity of cardiomyocytes, conventional static scaffolds are insufficient to restore the damaged electrophysiological microenvironment. In recent years, the integration of 3D printing technology with electrical stimulation has emerged as a highly promising bioengineering strategy for reconstructing cardiac electrical conduction networks, modulating cellular electrophysiology, and restoring contractile function.

In the early exploration of cardiac tissue engineering, researchers attempted to exploit electrical stimulation to investigate the role of electric fields in promoting the in vitro maturation of cardiomyocytes. In 2017, Adams *et al.*[157] employed 3D printing to fabricate three-dimensional cell culture scaffolds with controlled pore architectures using PCL and silicone rubber as substrate materials. A multichannel external electrical stimulation system capable of wireless control via smartphone was developed, wherein graphite rod electrodes positioned within culture wells delivered localized pulsed electric fields to the insulating scaffolds. Results demonstrated that PCL scaffolds exhibited superior cytocompatibility; furthermore, under external electrical stimulation at 5 V and 1 Hz, primary human cardiomyocytes (pHCM) seeded on these scaffolds displayed markedly elevated cell density, with a substantial proportion of cells exhibiting prominent cytoplasmic actin pseudopodial extensions, thereby confirming the constructive role of electric field intervention in promoting cardiomyocyte structural differentiation (Figure 10a).

Despite the efficacy achieved through external electrical stimulation, ideal cardiac repair materials should possess intrinsic electrical conductivity and recapitulate the highly organized anisotropic architecture of native myocardium. To this end, Ul Haq *et al.*[158] employed 3D micro-stereolithography to precisely fabricate conductive scaffolds mimicking the hierarchically aligned lamellar organization of myocardial muscle fibers, as illustrated in Figure 10b. The photocurable conductive bioink consisted of a ternary composite of photosensitive PEGDA, the conductive polymer PANI, and curcumin serving as a light-absorbing photoinitiator dye. The incorporation of curcumin functioned as a liquid optical filter, effectively regulating light penetration depth and ensuring high-fidelity resolution during 3D fabrication. The resulting biomimetic scaffold not only exhibited a

well-defined microstructured architecture but also demonstrated favorable semiconducting properties, supporting ionic diffusion and electron transfer between the polymer matrix and the surrounding electrolytic medium, thereby providing cardiomyocytes with a conducive biomimetic conductive interface.

To translate such in vitro conductive scaffolds toward in vivo orthotopic therapeutic applications, the development of implantable conductive cardiac patches with high flexibility and tissue compliance has become a critical objective. In 2024, Luque *et al.*[159] designed a printable conductive cardiac patch based on PEDOT for myocardial tissue remodeling, as depicted in Figure 10c. The hydrogel matrix, composed of PVA, PEDOT, and gallic acid as a supramolecular dynamic crosslinking agent, demonstrated exceptional elasticity, mechanical robustness, and thermoreversible phase transition characteristics, rendering it well-suited for direct-write 3D printing via melt extrusion. In adult murine models, the patch efficiently conducted electrical pacing signals with ultralow impedance to trigger intracellular calcium transients without inducing any malignant arrhythmias following epicardial implantation. Crucially, magnetic resonance imaging monitoring revealed that the patch provided both mechanical support and electrical conduction pathways to the infarcted myocardium, significantly improving left ventricular ejection fraction and stroke volume.

The aforementioned approaches frequently rely on lead implantation or conductive networks to transmit external pacing signals, which may cause secondary physical injury or foreign body responses. To fundamentally overcome these limitations, Ershad *et al.*[126] proposed a passive, wireless cross-scale heterogeneous integration strategy in 2025, as shown in Figure 10d. Solid-state microscale solar cells (μ-solar cells) fabricated via micro/nanofabrication processes were physically dispersed as discrete microfillers within gelatin methacryloyl (GelMA) hydrogel, constructing a novel class of photoelectroactive bioink. Through extrusion-based 3D printing, this bioink was co-cultured with cardiomyocytes to form three-dimensional cardiac constructs with light-responsive electrophysiological characteristics. Upon illumination at specific wavelengths, the embedded μ-solar cells instantaneously convert photonic energy into localized microcurrents *in situ*. This electrical stimulation mechanism, based on the physical integration of devices, has successfully enabled the wireless and on-demand pacing of

cardiac tissue beating rhythms, opening up highly futuristic application prospects for next-generation smart cardiac patches and fully non-invasive bioelectronic devices.

The synergistic strategy combining 3D printing and electrical stimulation has achieved notable progress in repairing tissues such as skin, nerve, bone, and myocardium, and shows broad therapeutic potential. With next-generation high-precision printing technologies and intelligent bioinks on the horizon, this approach is expected to overcome current interdisciplinary challenges and extend its applications to more complex pathological scenarios.

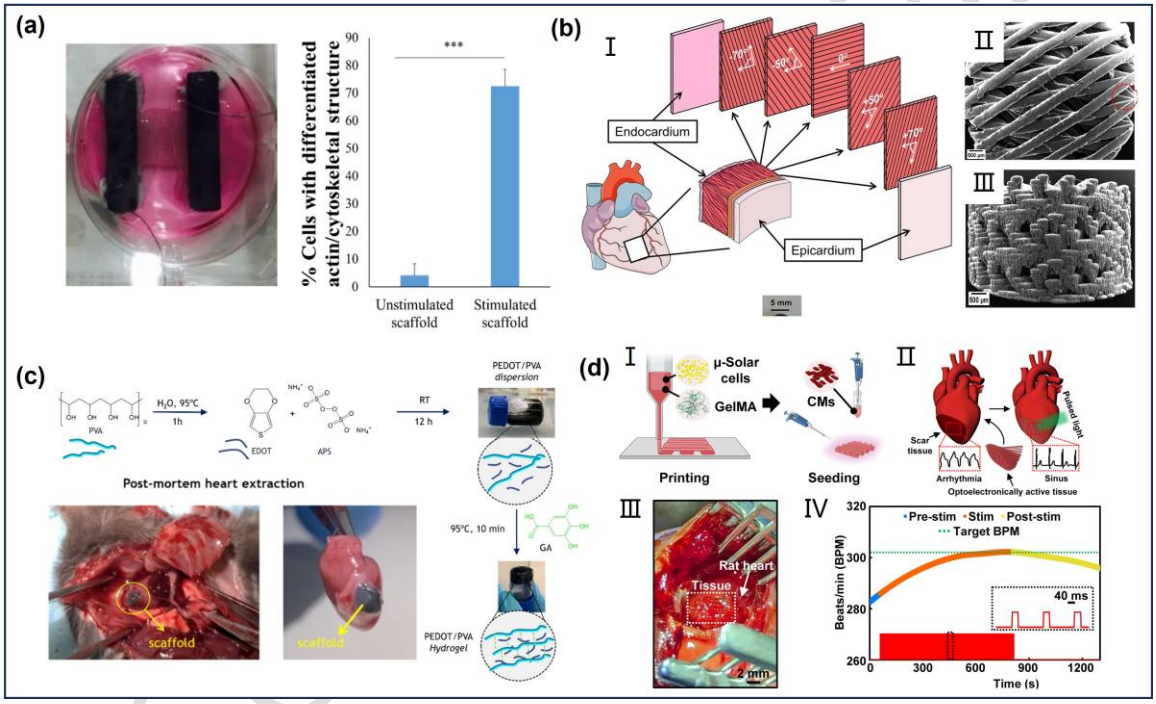

Figure 10. Applications of 3D-printed electroactive scaffolds and diversified electrical stimulation strategies in cardiac tissue engineering. (a) Schematic illustration of electrical stimulation of primary human cardiomyocyte on a PCL-based scaffold (left). A graph showing the percentage of cells with differentiated actin structure in both stimulated and unstimulated tests (right). Reprinted with permission from Ref.[157] Copyright© 2017 Elsevier B.V. (b) Schematic diagram of the myofibrils in myocardium and printed scaffolds. (I) The myofibers are oriented at different angles in a hierarchical manner. (II)&(III) SEM diagram of the printed scaffold. Modified and reprinted with permission from UI Haq et al.[158] Copyright© 2023 Springer Nature. (c) Schematic diagram of the PVA-GA/PEDOT

hydrogel preparation process and the conductive scaffold applied to the heart. Reprinted with permission from Ref.[159] Copyright © 2024 American Chemical Society. (d) Schematic diagram of a 3D-printed optoelectronic scaffold for cardiac pacing. (I) Schematic diagram of a 3D-printed optoelectronic scaffold. (II) Example of in vivo implantation of a printed optoelectronically active tissue and correction of arrhythmic beating. (III) Schematic diagram of the optoelectronically active tissue on the rat heart surface. (IV) Beating rate of rat hearts following optoelectronic stimulation. Modified and reprinted with permission from Ershad et al.[126] Copyright© 2025 AAAS.

6. Conclusion and future perspectives

Although combining 3D bioprinting with ES shows great promise for repairing complex tissue defects, several technical challenges must be addressed before clinical use. First, the precise molecular pathways by which ES governs tissue repair need to be further elucidated. Different tissues respond differently to different electrical characteristics such as frequency, intensity and waveform. Further studies are needed to clarify the underlying mechanisms by which cells transduce external electrical inputs into intra-cellular responses via membrane receptors.[40] Second, current 3D printing technologies face difficulties in balancing high-resolution hierarchical structures with mechanical strength. Particularly challenging is the fabrication of large scaffolds with uniformly distributed conductive networks, as uneven current distribution can readily damage cells.[56] Third, an ideal scaffold must not only maintain stable electrical activity during the regeneration process but also be capable of eventual degradation in the body. However, conventional conductive polymers such as PEDOT:PSS and PPy lack intrinsic biodegradability and are prone to charge decay in physiological environments. Therefore, developing novel electroactive materials that can degrade safely without compromising a stable conductive network remains a significant challenge.[83,160]

Looking forward, ongoing research will help fully clarify the molecular mechanisms by which ES promotes tissue repair. Driven by rapid advances in integrated circuits and bioelectronics, future ES systems will become highly miniaturized and intelligent, enabling adaptive, high-precision modulation of electrical signals tailored to different tissues and

regenerative stages.[161] In biofabrication, further developments in 3D bioprinting will enable the precise creation of native micro- and nano-architectures, including dense capillary networks, which ensures a seamless integration of the printed scaffold with the host tissue.[162] In materials science, future conductive bioinks will not require a bulky external power source. Scaffolds will be made self-powered micro-generators through the incorporation of piezoelectric, triboelectric, magnetoelectric, bio-battery, or optoelectronic nanomaterials that harvest mechanical, magnetic, biochemical, or light energy.[163,164] In addition, advanced bioinks are also expected to achieve temporal programmability, enabling controlled modulus changes or on-demand release of growth factors at specific healing stages, potentially aided by 4D printing strategies and AI-guided formulation design.[165] Finally, developing fully biodegradable electroactive materials that safely degrade in sync with new tissue formation remains the critical step toward clinical success.[166]

In summary, the paradigm of integrating 3D printed conductive scaffolds with ES has shifted from passive physical support to active electrophysiological guidance. The combination of materials science, biofabrication and bioelectronics will soon enable this area to progress beyond the simple bridging of tissues toward the construction of fully smart, synthetic tissues. Through the precise spatiotemporal control of both electrical signals and material properties, we are on the verge of realizing the functional restoration of complex organs, thereby opening a new chapter in regenerative medicine.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

Not applicable.

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