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Review

Advances in bioelectrochemical technologies and electroactive bacteria for healthcare

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ABSTRACT

Bioelectrochemical systems (BESs) exploit microbial electroactivity to convert biochemical energy into bioenergy and are classified into three main types: microbial fuel cells (MFCs), microbial electrolysis cells (MECs), and microbial electrosynthesis cells (MESs). MFCs generate electricity from organic substrates, MECs rely on an external voltage for hydrogen production, and MESs direct cathodic electrons toward the synthesis of valuable biomaterials. Translating these BES modalities into biomedical contexts enables the development of versatile platforms capable of generating electricity for wearable devices or serving as auxiliary power sources for implantable electronics. In addition, BESs can support localized therapeutic functions, enable in situ production of bioactive molecules, monitor physiological parameters, and assist in managing clinical waste through self-sustained operation. This review presents the biological foundations and operational principles of BESs, emphasizing their evolution from energy-generating prototypes to wearable biomedical platforms. It discusses recent advances in BES-based biomedical applications, highlights existing challenges, and proposes future directions for sustainable bioenergy recovery and self-powered diagnostic and therapeutic devices.

1. Introduction

Bioelectrochemical systems (BESs) represent an integration of microbiology, electrochemistry, and materials science to achieve a real-time electron transfer between bacteria and conductive interfaces [1–3]. The metabolism of electroactive bacteria, which are vital elements in these systems, transform biochemical energy from organic matter into electricity and accelerate the progress of redox reactions [4]. Driven by prospects of advances in sustainable power generation, environmental restoration, and biomedical applications, BESs attract strong research interest [5–8]. Initial studies of BESs demonstrated that some bacteria can generate electricity from organic substrates, thus unlocking opportunities in waste-to-power technologies [9]. BES technologies have since expanded to produce hydrogen [8], or other reduced chemicals [10] under applied voltage, which convert carbon dioxide or other feedstocks into value-added biomaterials. The key characteristic of BESs is their integration of biological entities with electrodes and electronic elements, creating a biotic–abiotic interface capable of producing or sensing signals independently of traditional batteries or sophisticated energy supplies [11].

Fig. 1 illustrates the fundamental principles, technological evolution, and emerging biomedical directions of BESs. The core of BES operation is the extracellular electron transfer (EET) by electroactive bacteria, which enables electrons generated by bacterial metabolism to be exchanged with solid electrodes [3]. EET occurs via multiple mechanisms, including direct transfer through outer-membrane redox proteins, conduction along conductive pili or nanowires, and mediated transfer via endogenous or exogenous redox-active molecules acting as electron shuttles (Fig. 1A) [12]. Early demonstrations of microbial electricity generation date back to the work of Potter in 1911, who first showed that bacteria could generate current from organic substrates [13]. Subsequent studies advanced BES architecture with double

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chamber and single chamber designs, enhancing bioenergy output and simplifying operation [14]. Advances in microfabrication enabled the miniaturization of BESs into microfluidic platforms, where laminar flow supported membrane-free operation and precise mass transport [15]. More recently, paper-based [16] and textile-integrated BESs [5] were developed for direct operation in physiological fluids, enabling wearable devices (Fig. 1B). Miniaturized BESs initially demonstrated that physiological fluids such as sweat [7], saliva [17], blood [18], tears [19], urine [20], and wound exudates [21] can power small implants or biosensors. Progress in microfabrication and biocompatible material science provided the foundation of flexible BESs suitable for long-term operation in biological environments [22].

Apart from power generation, BESs also perform as biosensors and therapeutic tools, tracking metabolic indicators [1] or administering targeted electrical stimulation to promote tissue regeneration [21] (Fig. 1C). The incorporation of BESs into wearable and textile-based platforms, where biofilms simultaneously act as bioenergy generators and biosensors [23–25], contribute to the development of self-sustaining, non-invasive bioelectronic systems for personalized healthcare [26–28]. Electroactive bacteria can respond not only to chemical gradients but also to applied electric and magnetic fields, enabling controlled motion, orientation, and functional behavior [29,30]. Recent advances extended BES concepts to robotics and introduced electroactive bacteria as capable microrobotic systems with self-directed locomotion, real-time sensing, and localized therapeutic functions [31,32]. These living machines represent early prototypes of 'intelligent' biohybrid microrobotics, where microbial metabolism directly interfaces with electronic components for coordinated functions.

Despite significant advances, the translation of BESs into healthcare applications remains limited by several key challenges. The power output of many BES platforms remains insufficient for continuous operation of implantable or wearable medical devices [33]. BES-based biosensors are further constrained by limited selectivity and sensitivity [34,35], reducing their ability to accurately detect target biomarkers in complex biological fluids. Research on BES-based hydrogen generation in healthcare contexts remains limited, with few studies investigating biohydrogen production in physiologically relevant biofluids. [36,37]. Moreover, systematic preclinical evaluations are still lacking, hindering assessment of therapeutic efficacy, safety, and integration with biomedical applications. Although BES technologies can support the formation of basic metabolites, production titers remain low, and the synthesis of structurally complex, high-value therapeutics is constrained by metabolic pathway limitations and electron transfer losses [38,39]. Additionally, biocompatibility issues may constrain BES integration with biological tissues and fluids [40], and the long-term stability of BES depends on the durability of anodic biofilms [41] and the materials used for BES component fabrication [42,43]. Addressing these limitations is essential to advance the applications of BES in sustainable biomedical power generation, biosensing, and therapeutics.

Aiming to capture the state of the art and future potential of BES-based healthcare platforms, this review details the core mechanisms and biological components underlying BESs and highlights how the principal modalities are being adapted for medical contexts. This review is motivated by unmet clinical needs, including sustainable power for medical devices, real-time reagent-free biomarker monitoring, energy-efficient wastewater treatment, and scalable on-demand therapeutic production. Within this context, the distinct roles of BESs are clearly delineated, highlighting their use in self-powered electronics and waste-to-energy conversion, hydrogen-mediated redox and therapeutic applications, and medical biomanufacturing. The review also discusses the evolution from power generator prototypes toward wearable platforms, recent advances in electronic textiles (*E*-textiles), biosensing, and biohybrid systems, and it critically evaluates outstanding knowledge gaps. In contrast to existing reviews that treat BES modalities or applications in isolation, this review aims to provide an integrated healthcare-focused framework linking power generation, diagnostics,

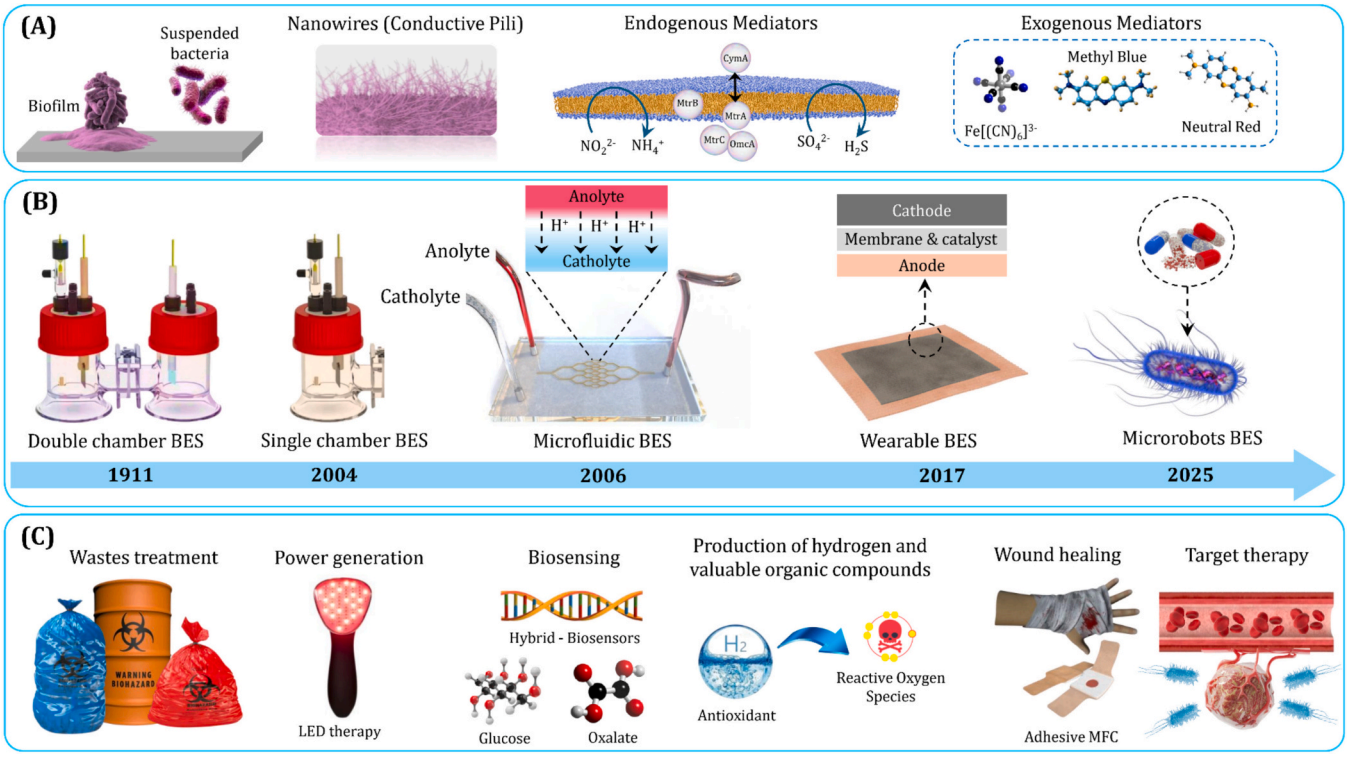

Fig. 1. (A) Extracellular electron transfer in electroactive bacteria occurs via conductive nanowires or endogenous and exogenous mediators, with cells suspended in the anolyte or attached to electrodes. (B) The evolutionary trend of bioelectrochemical systems (BESs), from double-chamber setups and early microbial electricity generation to biohybrid microrobots for targeted therapeutic delivery. (C) Biomedical BES applications include clinical waste treatment, wearable power sources, biomarker biosensing, reactive oxygen species (ROS) neutralization, wound healing, and targeted drug delivery.

biomanufacturing, and emerging biohybrid systems. This perspective facilitates critical assessment of translational barriers and research gaps to advance BESs into clinically relevant platforms for diagnostics, therapy, and health monitoring.

2. Basic principles of bioelectrochemical systems

2.1. Mechanisms of BES operation and the role of electroactive bacteria

The minimal functional unit of a BES comprises an anode (bacteria–electrode oxidation interface), a cathode (reduction interface), and an ion-conductive path (electrolyte and/or ion-exchange membrane) that preserves electroneutrality [3]. Bacteria at the anodic side degrade organic substrates via catabolic pathways, which result in oxidation products and the production of electrons, protons, and possibly additional ionic species. Electrons reduce the terminal acceptor at the cathodic side, while counter-ions migrate through the electrolyte and perm-selective membrane to balance the charge [44].

Electroactive bacteria, as the main elements of BESs, mediate extracellular electron transfer through two distinct mechanisms: direct electron transfer, and indirect electron transfer [12] (Fig. 1A). Examples of electroactive bacteria include both Gram-negative and Gram-positive species. Gram-negative bacteria such as *Shewanella oneidensis* and *Geobacter sulfurreducens* are the most widely studied, while Gram-positive examples include *Enterococcus faecalis* and certain *Listeria* and *Bacillus* strains [45]. Direct electron transport occurs via outer membrane cytochromes [46], or via conductive pili [47], which link cellular metabolism to terminal electron acceptors. The OmcZ and OmcS cytochromes are central to this process in *Geobacter sulfurreducens* [48], in contrast to *Shewanella oneidensis*, which uses the MtrCAB complex [49]. In contrast, indirect electron transfer occurs through soluble redox mediators that facilitate electron exchange between bacterial cells and terminal acceptors [50]. Endogenous mediators, such as flavins produced by *Shewanella oneidensis* [51], phenazines from *Pseudomonas aeruginosa* [52], and humic substances secreted by *Geothrix fermentans* [53], as well as exogenous ones such as methylene blue [54] and neutral red [55], facilitate electron transfer to terminal acceptors. Electron transfer mechanisms are critical for high-current applications. *Shewanella oneidensis* performs direct electron transfer via flavin-mediated endogenous pathways [51], whereas *Escherichia coli* relies on indirect, exogenous quinone-mediated electron transfer [56]. Comparative studies show that *S. oneidensis* achieves approximately 76,000 mA m^{-2}, while *E. coli* reaches approximately 19,200 mA m^{-2}, illustrating the higher electron transfer efficiency of organisms with native extracellular electron transfer pathways [57]. Genetic modification of electroactive microorganisms can enhance extracellular electron transfer (EET) through several mechanisms. Overexpression of outer-membrane cytochromes or conductive pili can strengthen direct electron transfer pathways. In addition, engineered biosynthetic pathways for redox mediators can facilitate indirect electron transfer by promoting electron shuttling between cells and electrodes [58]. Through precise manipulation of redox metabolism and membrane protein composition, modern genome editing technologies facilitate the design of electroactive bacteria optimized for transfer efficiency, versatility, and specific operational role [59].

2.2. Biofilm–electrode interface

Electroactive biofilms are heterogeneous conductors. Their architecture, cell density, extracellular polymeric substances (EPS), and conductive appendages collectively regulate electron percolation and substrate transport. These structural features also influence local physicochemical conditions, such as pH and redox potential [4]. The performance and stability of these biofilms are intrinsically linked to the properties of the underlying electrode interface [58]. Electrode material and surface chemistry are decisive for BES performance. High–surface-area carbon-based electrodes (e.g., carbon cloth, carbon nanotube, or graphene composites) [60] are chosen for their combination of excellent electrical conductivity, large effective surface area, and biocompatibility, which enhance microbial adhesion and biofilm density. Metal electrodes such as zinc, gold, and platinum [2] provide efficient redox coupling and rapid electron collection, while conductive polymers (such as hydrogels, Poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS), polypyrrole) [61,62] offer mechanical flexibility and surface tunability, enabling modulation of interfacial charge transport and biofilm adhesion. These materials collectively balance electrical conductivity, biocompatibility, and sustainability in BES design. Surface functionalization through peptides, polysaccharide films, and nanoscale modifications play a crucial role in improving electrode biocompatibility, reducing cytotoxicity, and regulating interfacial charge transport. Accumulation of extracellular debris, biofilm detachment, and surface fouling caused long-term signal drift and reduced device durability, emphasizing the need for precise control of shear stress, nutrient flux, and interfacial chemistry [42].

Electron transfer in BESs is governed by coupled thermodynamic, kinetic, and transport processes that set current density, energy efficiency, and overall performance [63,64]. The theoretical cell potential is derived from the Gibbs free energy of microbial redox reactions, and it can be described by the Nernst equation, which relates redox potential to the activities of substrates, products, and protons at the bacteria–electrode interface [65]. At the anode, extracellular electron transfer is driven by differences in redox potential between intracellular electron donors (e.g., the $NADH/NAD^+$ redox couple; NAD^+ = nicotinamide adenine dinucleotide, NADH = its reduced form) and the anode potential [66,67]. Interfacial charge-transfer kinetics, described by the Butler–Volmer equation, give rise to the activation overpotential, which represents the additional potential required to extract electrons from bacteria and oxidize the substrate [68]. Electron transfer occurs through conductive biofilms and through soluble mediators produced by suspended bacteria, with substrate consumption and mediator dynamics influencing overall performance [65]. At the cathode, reaction thermodynamics depend on the BES application (electricity generation, hydrogen evolution, or metabolite synthesis) and govern the reduction of oxygen, protons, or carbon dioxide, while mass transfer limitations also affect overall performance [69]. The presence of activation overpotential at both electrodes highlights the importance of electrode selection and catalyst integration for stable operation under physiological conditions [70]. The effective operating potential of a BES is further reduced from the theoretical cell potential by ohmic overpotential arising from ionic resistance in the electrolyte, membrane, and biofilm, as well as by concentration overpotential resulting from mass transfer limitations of substrates or protons [68]. Transport phenomena play a critical role in current generation. Suspended bacteria are influenced by advection, diffusion, and chemotaxis, whereas biofilm-associated bacteria are constrained by reaction and diffusion within the extracellular polymeric matrix [71]. Local substrate depletion and proton accumulation decrease microbial metabolic rates, thereby increasing both concentration and activation overpotentials [72].

These overpotentials collectively define BES performance, providing a framework for benchmarking through electrical parameters such as open-circuit potential, current density, power density, Coulombic efficiency (the fraction of electrons from substrate oxidation recovered at the anode), impedance, and internal resistance [73]. For other BES modalities, additional performance metrics such as hydrogen production rate [74] and metabolite synthesis rate [38] are included alongside these parameters. Biofilm–electrode impedance, measured by electrochemical impedance spectroscopy, characterizes charge-transfer resistance and biofilm maturity, whereas stability metrics (signal drift, detachment, fouling) determine device lifespan [75]. In biosensing applications, signal-to-noise ratio, response time, sensitivity, selectivity and detection limits become equally important, as small fluctuations in metabolic activity must produce resolvable electrical signals [76]. Importantly, these parameters face stricter constraints in biomedical

applications, where factors such as electrolyte conductivity, oxygen availability, substrate flux, and biocompatible materials limit performance compared to BESs used in wastewater or environmental applications.

2.3. Translating principles of BESs into biomedical applications

BESs utilize microbial metabolic activity to oxidize organic substrates, which results in the generation of electricity, hydrogen, and value-added products. The terminal electron acceptors capture released electrons to directly produce electricity, use them to reduce protons into hydrogen, or direct them toward the reduction of carbon dioxide to synthesize valuable compounds such as acetate, ethanol and butyrate. Based on the nature of their products, BESs are classified into three system types: microbial fuel cells (MFCs), microbial electrolysis cells (MECs) and microbial electrosynthesis cells (MESs). The bioelectrochemical process supports direct electricity generation from organic compounds in MFCs [77], or uses MECs operating under an external power source to induce hydrogen production [8]. MESs exploit cathodic electron flow to produce biomaterials or reduced chemical compounds, which links microbial electron transfer to controlled biomanufacturing and chemical synthesis [78]. The visual representation of BESs basic principles is as illustrated in Fig. 2:

Translating different BESs modalities into biomedical contexts creates versatile platforms that generate electricity to power wearable devices, provide localized therapy, produce in situ bioactive molecules, monitor key physiological parameters, and establish self-sustained platforms to manage hazardous clinical waste. In these settings, BESs convert endogenous or externally supplied organic substrates, such as glucose, lactate, acetate, or wound exudates, into electrical or chemical outputs [6,7,21,24,79]. Substrate-driven operation allows continuous energy harvesting and long-term autonomous function under physiological conditions of temperature, ionic strength, and pH. The electron-transfer dynamics that mediate energy conversion also form the basis for analytical and sensing performance. Fluctuations in current or potential correspond to substrate conversion and metabolic reactions occurring at the bacteria–electrode interface, which produce real-time electrical indicators of biochemical behavior. Mechanistically, variations in substrate concentration, oxygen availability, or redox balance affect intracellular electron carriers (e.g., NAD^+/NADH and flavins [80]) and extracellular electron transfer pathways, including outer membrane cytochromes, conductive pili, and soluble redox mediators [81]. These changes directly affect electron flux to the electrode, resulting in quantifiable electrical signals [82]. These responses correlate with clinically relevant parameters, such as glucose, lactate, pH, or infection markers, since these factors regulate bacterial metabolic activity and modulate electron-transfer rates at the interface [83]. This coupling between metabolism and electrical output enables BES based biosensors to operate as self-powered platforms capable of continuous, real time monitoring without external power supplies facilitating deployment at the skin interface and minimally invasive systems [84]. BES-based bioremediation exploits microbial metabolism of electroactive bacteria to oxidize toxic organics and/or reduce metal ions within anolyte simultaneous waste treatment and energy extraction [85]. When adapted to biomedical environments, this principle enables localized detoxification at wound sites, implant surfaces, or extracorporeal circulation systems, where controlled microbial redox reactions facilitate the degradation of inflammatory metabolites, uremic toxins, or excess reactive oxygen species [21,86]. By maintaining redox homeostasis, BES driven processes can mitigate tissue damage and support healing in compromised physiological environments [21]. This concept offers strategies for metabolic toxin removal, reactive oxygen species neutralization, and in situ decomposition of injurious biomolecules, which supports the development of healthcare devices, such as self-regenerating dressings and detoxification systems [85,87]. Collectively, these mechanisms position BESs as multifunctional biohybrid platforms that integrate energy conversion, biochemical sensing, and therapeutic action within a single, self-regulated system, enabling new paradigms for sustainable and intelligent biomedical technologies.

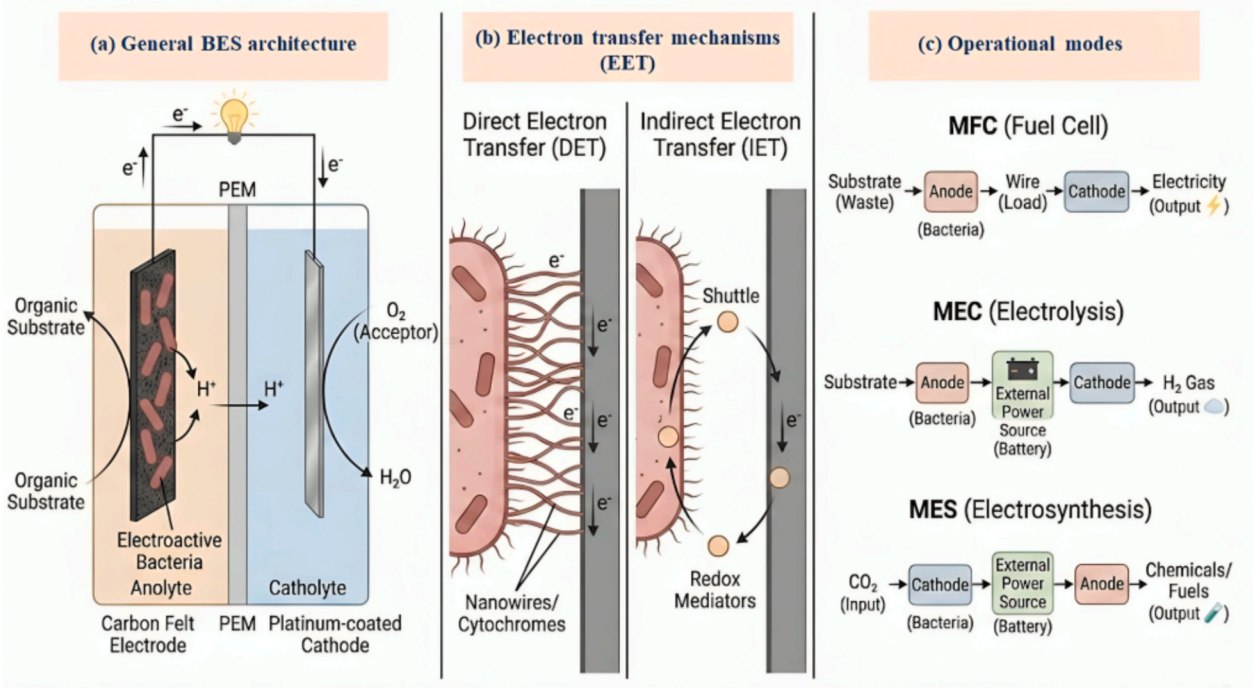

Fig. 2. Schematic overview of bioelectrochemical systems (BESs). (A) General architecture of a double chamber BES showing the anodic oxidation of organic substrates by electroactive bacteria, proton migration across a perm-selective membrane, and cathodic reduction of terminal acceptors. (B) Mechanisms of extracellular electron transfer (EET): direct electron transfer (DET) via outer membrane cytochromes or conductive pili (nanowires), and indirect electron transfer (IET) mediated by soluble redox shuttles. (C) Operational modes: MFCs for electricity generation, MECs for hydrogen production, and MES for chemical synthesis.

3. Microbial fuel cells for biomedical power generation

The integration of MFCs into biomedical systems could offer a sustainable route for energy generation at the biology–electronics interface [88]. Unlike conventional alkali-ions batteries, MFCs can use organic substrates available in biological fluids or biomedical waste, to provide continuous and renewable electricity production without toxic materials or frequent replacement [89]. Their steady, low-power output can effectively sustain the function of miniaturized medical tools such as biosensors, microfluidic pumps, and electrochemical drug-release systems, which provide self-powered therapeutic and diagnostic applications [90]. When coupled with energy storage systems, MFCs can be a maintenance-free power source for long-term health monitoring and localized medical interventions. The theoretical open-circuit potential (OCP) of MFCs is 1.01 V and employing with metal-based electrodes such as zinc achieved up to 1.4 V using *Shewanella oneidensis* [57]. With current and power densities of 42 mA cm^{-2} and 10.2 mW cm^{-2}, respectively, this microorganism obtained the highest output among tested strains, which is adequate to supply power to implantable medical devices (IMDs) [91]. Recent MFC advancements outline three promising biomedical configurations: biofluid-powered devices [7], bio-clinical waste-fed systems [92], and hybrid bioelectronic designs [93], all contributing to sustainable electricity solutions for next-generation clinical devices.

3.1. Biofluid-powered MFCs

This configuration focuses on physiological fluids derived from humans or animals, such as sweat [7], saliva [17], blood [18], tears [19], urine [20], and wound exudates [21], which contain oxidizable organic molecules that supports the metabolic activity of electroactive bacteria. Biofluid-powered MFCs are compatible with wearable [5] and skin-interfaced [94] applications.

3.1.1. Wearable MFCs

Wearable MFC designs utilize stretchable conductive materials or smart textile that maintain stable electrochemical interfaces under cultivation of electroactive biofilm [5]. Biocompatible substrates, such as cellulose conductive hydrogel, or biodegradable polymers, ensure safe skin contact, microbial growth, and comfort in wearable formats [26]. The first wearable MFC, fabricated on a textile platform, cultured *Pseudomonas aeruginosa* (which transfers electrons via endogenous mediators) in a flexible, membrane-less configuration comprising a 3D hydrophilic anode and an Ag_2O/Ag cathode, and produced power and current densities of 6.4 μW cm^{-2} and 52 μA cm^{-2}, respectively [95]. Examples of some studies demonstrating the performance of wearable MFCs are illustrated in Fig. 3. A wearable MFC integrated three MFCs and a solid-state supercapacitor on a single paper substrate, enabling simultaneous energy harvesting and storage from sweat (Fig. 3A) [7]. Wax printing and heat treatment defined the anodic and cathodic regions, with the intervening wax layer acting as an ion-exchange membrane. Pre-inoculated with *Bacillus subtilis*, the device generated 4 μW cm^{-2} and 37 μA cm^{-2}, stored 9.81 mF, maintained stable performance over more than 100 cycles, and delivered a constant discharge of 5.53 μAh. Based on sweat utilization, a paper-based wearable MFC employed *Bacillus subtilis* endospores as a biocatalyst, enabling long-term storage and repeated sporulation and germination in response to sweat, which naturally contains germinants. The device generated stable electricity (up to 24 μW/cm^2 and 175 μA/cm^2) without added nutrients, sufficient for small-scale wearable electronics (Fig. 3B) [24]. *Bacillus subtilis* also produces antibiotics that help maintain skin microbiota. Utilizing paper capillary-driven microfluidics, flexibility, and biocompatibility, the

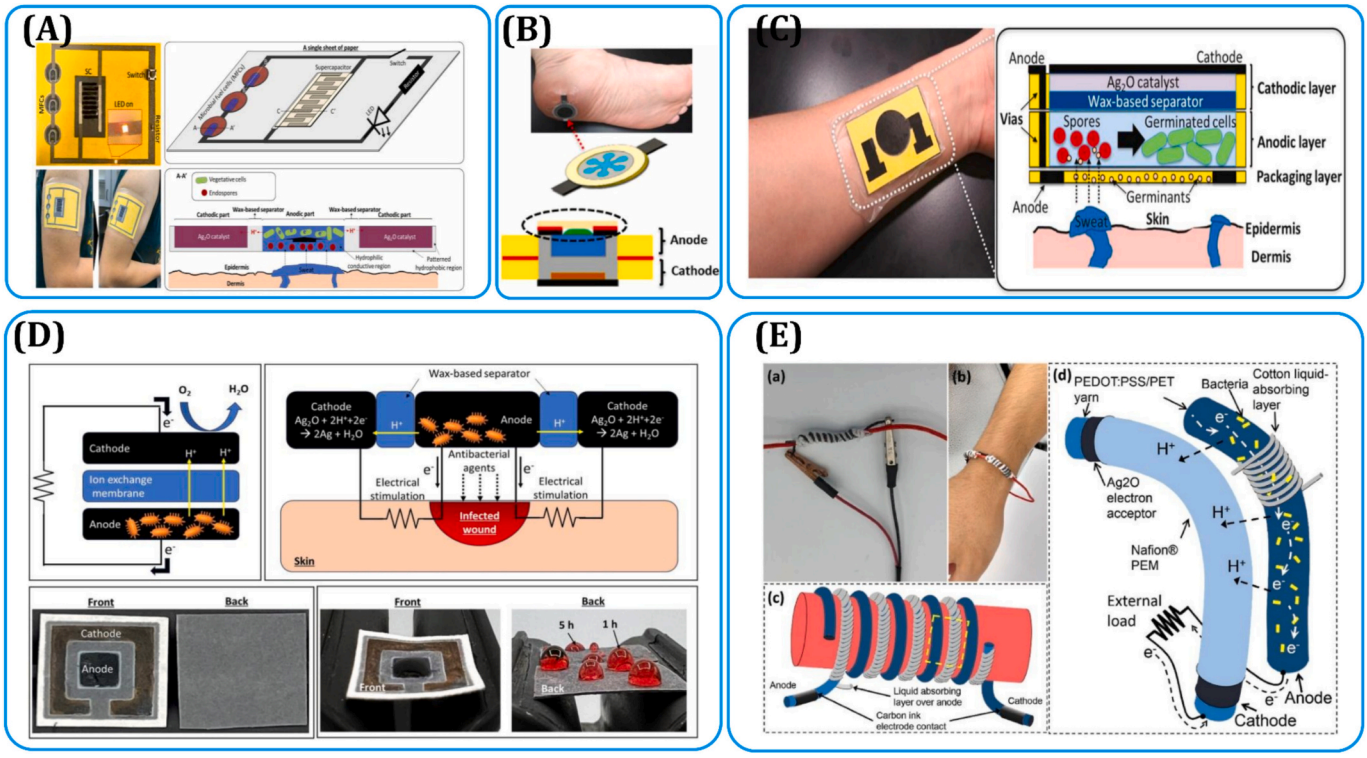

Fig. 3. (A) Wearable MFC and with supercapacitor devices generated a 4 μW/cm^2 from sweat by *Bacillus subtilis*. Adapted from [7]. (B) A sweat-activated MFC powered by *Bacillus subtilis* produced 24 μW cm^{-2} after 48 h of operation. Adapted from [24]. (C) A skin-mounted MFC inoculated with *Bacillus subtilis* achieved 16.6 μW cm^{-2}, with spore germination accelerated by nutrient germinants activated by sweat. Reproduced with permission from [79]. (D) A wearable wound dressing MFC used *Bacillus subtilis* endospores to generate electricity and antibacterial agents from wound exudate. Reproduced with permission from [21]. (E) A scalable yarn-based MFC utilizing PEDOT:PSS/PET conductive yarn and *Shewanella oneidensis MR-1* produced a power density of 22.12 W m^{-3} per single cell. Reproduced with permission from [6].

system provides a sustainable platform for wearable power, drug delivery, and skin-health monitoring, with performance influenced by individual sweat composition. In a similar structure, a skin-mountable MFC using *Bacillus subtilis* endospores as dormant biocatalysts was developed to generate electricity on demand from human sweat (Fig. 3C) [79]. Sweat and pre-loaded germinants triggered spore germination, producing an open-circuit voltage up to 1.25 V and a maximum power density of 56.6 μW/cm^2 from three devices in series. The endospores enabled long-term storage and safe disposal, while start-up time and long-term stability remained challenges.

Wearable MFCs were also applied for wound healing using a dressing containing *Bacillus subtilis* endospores that remained dormant until exposed to nutrient-rich wound exudate (Fig. 3D) [21]. Upon activation, the bacteria generated electricity and secreted antibacterial compounds. Tin oxide and copper oxide nanoparticles enhanced antibacterial activity and electron transfer. A conductive hydrogel-maintained moisture, supported bacterial function, prevented biofilm formation, and delivered electrical stimulation to accelerate wound healing. A flexible, scalable yarn-based biobattery demonstrated electricity generation through bacterial respiration (Fig. 3E) [6]. The system featured an anodic yarn functionalized with *Shewanella oneidensis* MR-1 and a cathodic yarn containing silver (I) oxide coated with Nafion as a proton exchange membrane. Power output could be tuned via yarn length or series/parallel connections, achieving current densities of 110–315 A m^{-3} and power densities of 19–22 W m^{-3}. This fiber form of the biobattery enabled integration into textiles through knitting, weaving, or embroidery, representing a significant step toward practical wearable electronics and IoT applications.

3.1.2. Skin-interfaced MFCs

Skin-interfaced MFCs represent a minimally invasive platform that extracts energy from skin biofluids such as interstitial fluid (ISF) or capillary blood [96]. Using microneedle-assisted interfaces [94], skin-interfaced MFCs efficiently draw glucose, lactate, and amino acids from ISF or capillary blood, supporting microbial activity and generating electricity [97]. Utilizing non-pathogenic electroactive bacteria is crucial for ensuring operational safety and broadening their suitability for therapeutic applications. To date, microneedle-assisted energy-harvesting platforms have been demonstrated exclusively in enzymatic and abiotic biofuel cells, where immobilized redox enzymes catalyze substrate oxidation under well-controlled conditions [96]. In these systems, glucose- or fructose-driven enzymatic reactions enable localized power generation for transdermal biomedical functions.

3.2. Medical and hospital waste-fed MFCs

The conversion of organic-loaded biomedical and hospital waste into electricity is achievable through MFC systems [87]. Medical effluents, surgical wastewater, blood-contaminated fluids, and used culture media are biodegradable substrates for these systems [98]. For example, an MFC removed 95.3% of chemical oxygen demand, 97.1% of paracetamol, and 87.5% of diclofenac from hospital wastewater, and produced 42.93 mW/m^2 [85]. Electron extraction through bioelectrochemical reactions accelerates microbial metabolism and consequently organic biodegradation beyond that of conventional treatments [87]. These platforms can be implemented for extensive effluent purification establishing environmentally sustainable infrastructure for clinical and biomedical facilities. However, practical implementation necessitates careful consideration of biosafety, sterilization, and regulatory compliance to prevent hazards associated with pathogenic material handling.

Table 1 presents a comparative overview of selected MFC examples discussed above, categorized into wearable, textile-based, skin-interfaced, and clinical waste treatment applications. The table summarizes system configurations, biocatalysts or anode materials, operating biofluids or substrates, performance metrics, and associated functional objectives.

3.3. Hybrid bioelectronic MFC platforms

MFCs are being combined with innovative bioelectronic frameworks such as wound dressings and organ-on-chips platform and biohybrid robotic systems to expand interface functionality [93]. These hybrid systems combine MFCs with electronic or bioelectronic devices, using the electricity generated by bacterial metabolism for other functions such as sensing and electrostimulation. For example, electroactive biofilm incorporated into wound dressings can power healing sensors or promote tissue repair via low-voltage currents [21]. The coupling of MFCs with organ-on-chip systems provides in situ bioelectrical monitoring and exemplifies their capability to function as adaptive biointerfaces.

Evaluating the energy output of MFCs is essential when considering their integration with conventional biomedical devices. These devices include diagnostic systems for monitoring disease progression, therapeutic systems delivering electrical or neural interventions, and closed-loop platforms that adjust treatment based on sensor feedback [101,102]. These devices span a wide range of energy demands, with implantable and ingestible electronics typically requiring 200 nW to 250 mW. Low-power devices such as pacemakers (10–30 μW), deep brain stimulators (~100 μW), and intraocular pressure monitors (200 nW to 200 μW) operate in the microwatt range. Devices performing stimulation or imaging, including spinal or gastric stimulators (1–30 mW), wireless capsule endoscopes (5–30 mW), and retinal prostheses (~250 mW), represent the upper end of energy consumption [102].

Conventional electrochemical batteries remain the dominant power source in clinical practice. Non-rechargeable lithium batteries provide 500–1000 mWh cm^{-3}, with self-discharge times up to 10 years. Silver

Table 1
Selected MFC systems categorized by application, configuration, biocatalyst, substrate, and performance.

Configuration	Biocatalyst / Anode material	Biofluid / substrate	Performance *	Application / function	Ref.
Wearable & textile MFCs	*Pseudomonas aeruginosa*/3D hydrophilic textile	Sweat	P_{max} = 4 μW cm^{-2} I_{max} = 37 μA cm^{-2}	Sweat-driven disposable self-charging power generator	[7]
	Bacillus subtilis strain 168/ Conductive paper sheet	Sweat	P_{max} = 4 μW cm^{-2} I_{max} = 37 μA cm^{-2}	Hybrid self-powered sensing system	[99]
	Bacillus subtilis endospores /Hydrogel composite	Wound exudate	N/A	Self-powered infection monitoring & healing device	[21]
	Bacillus subtilis/ PEDOT:PSS & DMSO	Sweat	P_{max} = 24 μW cm^{-2} I_{max} = 175 μA cm^{-2}	Sweat-activated power generator	[24]
	Shewanella oneidensis MR-1/ PEDOT:PSS-PET yarn	L-broth (LB)	P_{max} = 22.12 W m^{-3} I_{max} = 315 A m^{-3}	Scalable yarn-based biobattery	[6]
Skin-interfaced	*Bacillus subtilis*/ Skin-mounted interface	Sweat	P_{max} = 16.6 μWcm^{-2}	Non-invasive spore-forming MFC	[79]
Clinical waste treatment	Mixed culture/ Graphite felt	Paracetamol	I_{max} = 238.3 μA cm^{-2}	Treatment of pharmaceutical wastewater	[100]

* P_{max} = Maximum Power Density, I_{max} = Maximum Current Density.

oxide batteries offer 400–800 mWh cm^{-3}, supporting ingestible devices with lifetimes of 5–7 years. Rechargeable lithium-ion batteries provide 90–240 milliwatt-hours per gram, 200–700 mWh cm^{-3} but require protection circuitry for safety [102]. Despite their maturity, batteries have limitations, including finite lifetime, replacement needs, leakage risk, and long-term biocompatibility.

These constraints have prompted exploration of in vivo energy harvesting approaches, using endogenous chemical sources such as glucose and hydrogen ions in blood, interstitial fluid, cerebrospinal fluid, and the gastrointestinal tract. In vivo biofuel and galvanic cells in animal and human studies have generated power densities of 2–200 μW cm^{-2} [103,104]. Although MFCs have not yet been tested in vivo, in vitro microfluidic systems using *Shewanella* species with zinc anodes have achieved 1.39 V and power densities exceeding 3500 μW cm^{-2}, demonstrating strong potential for future biomedical applications [57].

However, the in vivo feasibility of MFCs remains unproven, primarily due to challenges associated with maintaining stable, electroactive biofilms under physiological conditions. Long-term operation requires reliable nutrient availability, controlled microbial growth, and sustained electron transfer without biofouling or immune-mediated clearance. Host immune responses, variations in pH, oxygen, and metabolite levels, and mechanical disturbances can destabilize microbial activity and electrode interfaces. In addition, ensuring biocompatibility of electrodes, preventing infection, and achieving reproducible performance over clinically relevant timescales remain critical challenges that must be addressed before MFCs can be translated to medical applications.

4. Microbial electrolysis cells with biomedical and environmental benefits

The antioxidant and anti-inflammatory capabilities of molecular hydrogen (H_2) provide effective defense against oxidative injury, inflammatory activation, and ischemic damage in cardiovascular, neurological, and metabolic pathologies [105]. H_2 small size allows rapid diffusion across tissues, including the blood–brain barrier. Safe and versatile, H_2 can be administered via inhalation, hydrogen-rich water, or saline for therapeutic use [106]. The therapeutic potential of in situ hydrogen production for cancer using alkali batteries was reported [107,108]. For example, an implantable Zn/Mg–O_2 battery produced hydrogen and consumed oxygen within the tumor microenvironment inducing mitochondrial dysfunction, which enhanced the activity of hypoxia-activated prodrugs (HAPs), and resulted in over 99% tumor inhibition [107]. Building on hydrogen-mediated sensitization of tumors, the implantation of radioactive iodine-125 seeds was enhanced by developing an AZ31 magnesium alloy–based seed strand that enables pH-dependent, sustained hydrogen release while maintaining sufficient mechanical strength [108]. Hydrogen released from the strand synergistically enhanced the therapeutic effect of iodine-125 radiotherapy by inhibiting tumor proliferation, inducing apoptosis, disrupting redox and mitochondrial function, reducing ATP production, and impairing DNA repair. In preclinical studies, this combined system outperformed iodine-125 seeds alone without observable side effects, highlighting its potential to improve and broaden brachytherapy applications (Fig. 4A).

Extending this electrochemical hydrogen-generation paradigm to living catalytic systems, MECs enable hydrogen production through anaerobic bacterial oxidation coupled to electrode reactions at external potentials of 0.2–0.8 V, substantially lower than those required for

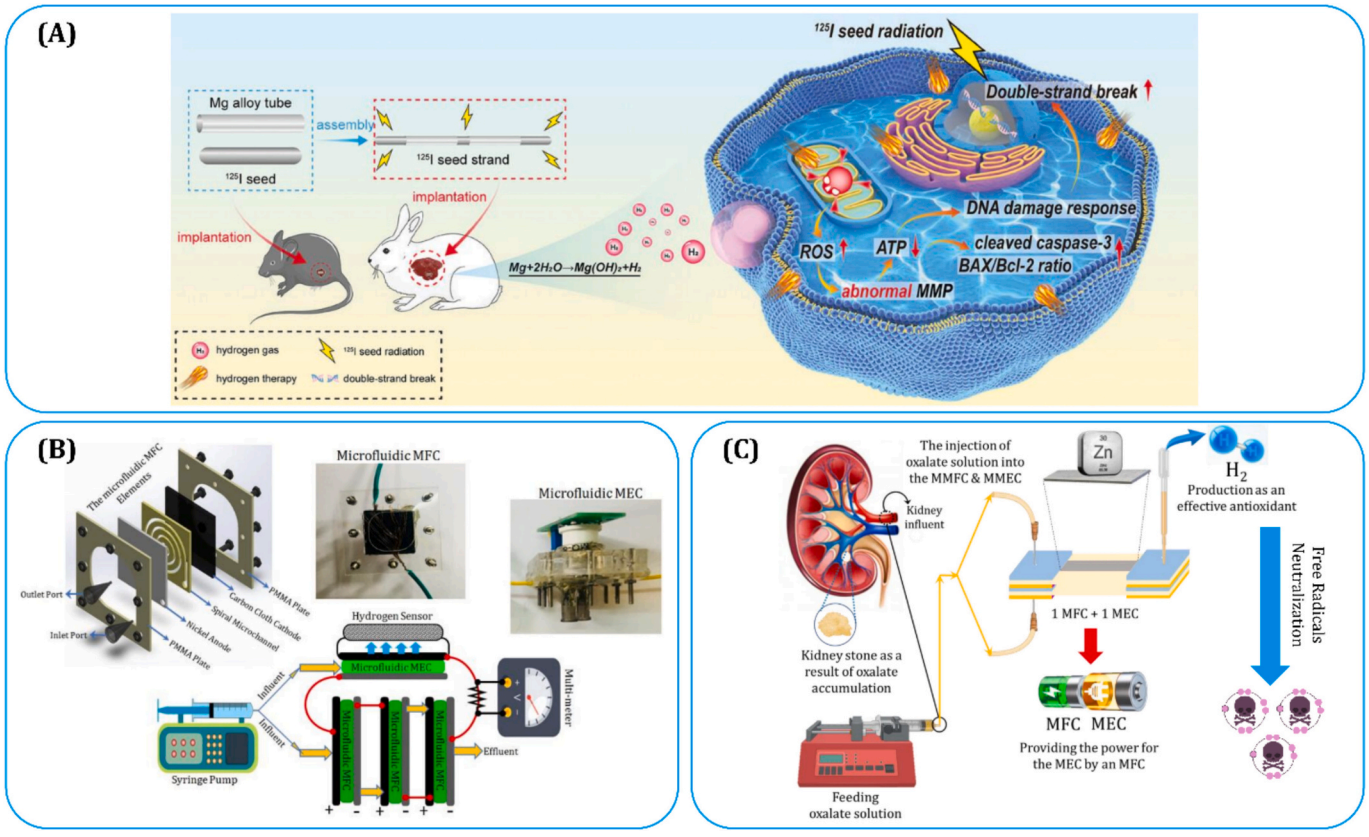

Fig. 4. (A) An AZ31 magnesium alloy iodine-125 seed strand (AMASS) releases hydrogen to enhance radiotherapy by promoting apoptosis, disrupting redox balance, and increasing DNA damage. Reproduced with permission from [108]. (B) A self-powered MEC integrated with three MFCs using *Escherichia coli* produced 1.97 V and hydrogen at 46 ppm h^{-1} from glucose and 28 ppm h^{-1} from urea [36]. (C) A microfluidic MEC–MFC system with a zinc anode and *Shewanella oneidensis* MR-1 achieved ~1.3 V and hydrogen production of 1.12 mol H_2 mol^{-1} day^{-1}, twelve times higher than a glucose-fed nickel system [5].

conventional water electrolysis (1.8–2.2 V) [8]. Certain microorganisms can increase hydrogen production beyond basic electron-driven proton reduction. Some types of fungi produce hydrogen via hydrogenase enzymes [109], though less efficiently than bacterial [110] or algal systems [111]. Under anaerobic conditions, fermentative bacteria such as *Clostridium butyricum* [112] and *Enterobacter aerogenes* [113] generate hydrogen by converting carbohydrates into organic acids catalyzed by hydrogenases [110]. *Desulfovibrio paquesii* DSM 16681 obtained the highest rate of hydrogen production (19 m^3 m^{-3} d^{-1}), compared to moderate rates of *Rhodobacter* spp. (3.6–6.25 m^3 m^{-3} d^{-1}) and lower rates from *Shewanella oneidensis* and *Geobacter sulfurreducens*, possibly due to limitations in hydrogenase activity and operational parameters [114].

Photosynthetic bacteria, such as *Rhodobacter sphaeroides* [115] and *Rhodopseudomonas palustris* [116], exploit nitrogenase activity to produce hydrogen. Additionally, *cyanobacteria* like *Anabaena* and *Nostoc* release hydrogen via nitrogenase or bidirectional hydrogenase during oxygenic photosynthesis [117]. The incorporation of these photosynthetic bacteria into wearable biohybrid devices supports hydrogen generation using light energy, CO_2, and sweat-based nutrients, promotes their applications for wound healing, reducing oxidative stress, health monitoring and offers a sustainable strategy through atmospheric carbon capturing instead of organic substrates.

The production of hydrogen was reported by algal species such as *Scenedesmus obliquus*, *Chlamydomonas reinhardtii*, *Chlorella vulgaris*, *Anabaena* sp., and *Nannochloropsis salina* [118]. Their cultivation within the catholyte of MFCs promotes photosynthetic oxygen generation and allows simultaneous production of electricity, hydrogen, biomass, and nutrient recovery [119]. Although the rate of hydrogen production for these algae-assisted MFCs is lower than that of conventional MECs, they hold promises for sustainable environmental remediation. For instance, the implementation of these systems for treatment of hospital wastewater allows reduction of nitrate and phosphate loads, mitigating public health risks. Additionally, the lipid-rich algae also provides renewable biomaterial sources, linking sustainable energy development with environmental remediation and public health benefits [120].

MECs can provide therapeutic hydrogen at both systemic and localized scales. At microfluidic and wearable levels, controlled hydrogen generation mitigates oxidative stress and inflammation, promoting wound healing, and ischemia–reperfusion recovery. A coupled microfluidic BES, combining two or three series of MFCs with a MEC with a spiral microchannel, was developed as a self-powered hydrogen generator using non-pathogenic *Escherichia coli* to produce hydrogen from glucose and urea at physiologically relevant concentrations. A three-MFC series achieved 1.97 V and 38.2 W m^{-3}, yielding 0.09 mol H_2 mol^{-1} substrate day^{-1} (Fig. 4B) [36]. In a subsequent study, *Shewanella oneidensis* MR-1 was replaced with *Escherichia coli*, and a straight microchannel was employed instead of a spiral design, with the zinc electrode replacing the nickel electrode (Fig. 4C) [37]. The comparison of the two systems showed that configurations employing *S. oneidensis* MR-1, which transfers electrons via nanowires, achieved markedly higher performance. Power density increased from 7.98 to 694 mW m^{-2}, while hydrogen production rose from 0.09 to 1.12 mol H_2 mol^{-1} day^{-1} when glucose was replaced with oxalate, a toxic kidney metabolite. These results underscore the advantage of native extracellular electron transfer mechanisms. Moreover, a single MEC was sufficient to generate the required hydrogen, eliminating the need for two MFCs to support power. These microfluidic systems demonstrate versatile, on-demand hydrogen delivery for biomedical applications.

Table 2 provides a comparative overview of discussed hydrogen-producing systems, highlighting differences in system configuration, biocatalysts, substrates, hydrogen production performance, and their corresponding biomedical or environmental applications.

To highlight clinical relevance, the hydrogen production of the optimized microfluidic MEC–MFC system can be compared with in vivo hydrogen concentrations achieved via inhalation in rats. H_2 saturation concentrations were monitored in different tissues after 500 s, with the highest in the kidney (28–509 μmol/L, depending on inhaled concentration of 4–67%), followed by the brain (26–485 μmol/L), liver (18–314 μmol/L), spleen (13–225 μmol/L), and lowest in the gastrocnemius muscle (6–161 μmol/L) [124]. A microfluidic MEC with a zinc anode and *Shewanella oneidensis* MR-1 produced 1.12 mol H_2 per mol substrate per day [125]. Considering a 50 μL MEC volume over 500 s, the corresponding hydrogen concentration reaches ~1.3×10^8 μmol/L, far exceeding physiological levels observed in animal studies. This demonstrates that MECs can deliver therapeutically relevant hydrogen doses in vivo, supporting applications in antioxidant therapy, oxidative stress mitigation, and targeted treatment of oxalate-related kidney conditions. While in vivo measurements reflect organ-level H_2 saturation, the MEC produces hydrogen in a concentrated microfluidic environment with bulk concentrations exceeding those in tissues, demonstrating its ability to reach therapeutically relevant doses after dilution in vivo.

Although studies of MECs as IMDs are currently limited, the use of MECs for localized therapeutic hydrogen production holds significant potential. Conceptually, wearable MEC platforms, as oxygen-independent configurations, could be designed to harness non-pathogenic electroactive bacteria such as *E. coli*, *S. oneidensis*, and *B. subtilis* for hydrogen production from physiological substrates (e.g., saliva, sweat, blood glucose, and excreta), but such applications remain for now largely exploratory. Unlike photocatalytic approaches [126], wearable MECs provide sustained antioxidant and anti-inflammatory effects through localized hydrogen delivery for neuroprotection, which mitigates oxidative stress implicated in Alzheimer's disease, and offering superior efficacy to inhalation or hydrogen-rich water [127]. In oncology, immunotherapy, and transplant applications, self-powered MECs offer sustainable hydrogen generation promoting antitumor immune responses and impairing tumor redox balance [128]. They can also utilize gut-derived short-chain fatty acids to generate hydrogen, restore microbiota balance, alleviate psychiatric symptoms, and offer a

Table 2
Representative hydrogen-producing electrochemical and bioelectrochemical systems with corresponding biomedical and environmental applications.

System Type	Biocatalyst / Material	Substrate / Input	H_2 Production / Performance	Biomedical / Environmental Goal	Ref.
In situ H_2 generation	Mg-Alloy	Anode oxidation	Tumor inhibition	Tumor inhibition via hypoxia-activated prodrug	[107]
Microfluidic MEC	*Escherichia coli* / Nickel anode	Glucose / Urea	0.09 μL H_2 μL (glucose)$^{-1}$ day^{-1}	Self-powered H_2 generation from human biofluids	[36]
	Shewanella oneidensis/ Zinc anode	Oxalate (Kidney metabolite)	1.12 μL H_2 μL (oxalate)$^{-1}$ day^{-1}	Removal of toxic metabolites (stones) & H_2 synthesis	[37]
Macro-sized MEC	Mixed culture / Graphite brush	Sodium acetate	3.12 μL H_2 μL (acetate)$^{-1}$ day^{-1}	First reported single chamber MEC	[121]
	Geobacter sulfurreducens / Graphite felt	Starch	0.13 μL H_2 μL (substrate)$^{-1}$ day^{-1}	Enhanced H_2 production by bioaugmentation with *Geobacter sulfurreducens* strain YM18	[122]
	Mixed culture / Carbon felt	Sodium acetate	72 μL H_2 μL (acetate)$^{-1}$ day^{-1}	High production rate of H_2	[123]

novel therapeutic strategy against opioid relapse via the gut–brain axis [129].

5. Microbial electrosynthesis systems for medical biomanufacturing

Biomanufacturing utilizes biological systems to produce chemicals, pharmaceuticals, and other value-added products sustainably from renewable resources [130]. Engineered BESs can biosynthesize functional materials for biomedical applications. Through adjustable control of anodic, cathodic, and electrosynthetic modules, MESs enable flexible and on-demand synthesis of bioactive and pharmacologically relevant substances [78]. On the anodic side of BESs, electroactive biofilms produce EPS as structural and functional components of microbial attachment and electron transfer. Within BES operation, EPS primarily contributes to biofilm cohesion, electrode colonization, and modulation of interfacial charge transport [12]. Several studies subsequently described the isolation and characterization of EPS from electroactive bacteria, showing antioxidant activity and cytocompatibility in in vitro assays, including activity against breast and colon cancer cell [131]. Importantly, while the biomedical applications of polysaccharide-based materials such as alginate, dextran, gellan, and hyaluronic acid are well established, their relevance here lies in the ability of BES-grown biofilms to act as renewable sources of EPS, rather than in direct therapeutic deployment. Post-processing approaches, including purification, chemical modification, and crosslinking, have been shown to enhance the mechanical stability and functional performance of EPS-derived materials for applications such as drug-delivery matrices [132], regeneration scaffolds [133], and wound dressings [134]. These studies indicate that BESs may function as bioelectrochemical production platforms for EPS with biomedical relevance, rather than as direct clinical delivery systems.

On the cathodic side, further opportunities for medical biomanufacturing are available where microalgae can function as biofactories capable of producing diverse bioactive compounds [135]. Non-pathogenic microalgae act as efficient biofactories, producing diverse bioactive compounds with therapeutic potential. *Chlamydomonas reinhardtii* is widely used for recombinant protein expression and carotenoid production [136]. *Porphyridium* spp. generate sulfated polysaccharides, phycoerythrin, and eicosapentaenoic acid (EPA), while *Spirulina* (*Arthrospira*) platensis provides phycocyanin, carotenoids, and bioactive peptides [137,138]. *Haematococcus pluvialis* predominantly yields astaxanthin [139], and marine species such as *Schizochytrium* and *Crypthecodinium* produce docosahexaenoic acid (DHA) [140]. These metabolites exhibit antioxidant, anti-inflammatory, immunomodulatory, and anticancer activities, highlighting microalgae as promising biofactories for medical applications. Table 3 highlights representative microalgae and their bioactive mechanisms across diverse biomedical applications, emphasizing their multifunctional roles in tissue regeneration, immune modulation, therapeutic delivery, and disease prevention. In tissue engineering, species such as *Porphyridium* sp., *Chlamydomonas reinhardtii*, and *Synechococcus* sp. are incorporated into hydrogels or photosynthetic scaffolds, promoting cell proliferation, angiogenesis, and tissue repair [141]. For drug delivery, *Thalassiosira weissflogii* and *Spirulina platensis* serve as nanocarriers, enhancing drug stability, enabling targeted delivery, and allowing controlled release [142]. Several species such as *Skeletonema marinoi*, *Micractinium* sp., *Chlorella vulgaris*, and *Dunaliella salina*, exhibit anticancer activities through apoptosis induction, cell cycle arrest, and modulation of oxidative stress and immune responses [137]. In immunomodulation, *Tribonema* sp., *Porphyridium* sp., and *Spirulina platensis* stimulate macrophages, regulate cytokine release, and enhance innate and adaptive immunity [138]. Microalgae such as *Arthrospira platensis* and *Nannochloropsis oculata* provide antidiabetic benefits by lowering blood glucose, improving insulin sensitivity, and regulating lipid metabolism [143]. Lastly, for cardioprotection, *Dunaliella salina*, *Tisochrysis lutea*, and *Nannochloropsis* sp. help improve lipid profiles, reduce oxidative stress and inflammation, and protect cardiac tissue [144].

Table 3
Representative microalgae and their bioactive mechanisms across diverse biomedical applications.

Application	Selected algae with functional targets	Bioactive role / mechanism
Tissue engineering [141]	*Porphyridium* sp. (skin wound healing), *Chlamydomonas reinhardtii* (oxygen-generating wound scaffolds), *Synechococcus* sp. (ischemic tissue repair)	Hydrogels and photosynthetic scaffolds enhance cell proliferation, angiogenesis, and tissue regeneration
Drug delivery [142]	*Thalassiosira weissflogii* (cancer drug carrier), *Spirulina platensis* (curcumin nanoparticle delivery)	Nanocarriers improve drug stability, allow targeted delivery and controlled release
Anticancer [137]	*Skeletonema marinoi* (colon anticancer), *Micractinium* sp. (breast anticancer), *Chlorella vulgaris* (liver anticancer), *Dunaliella salina* (leukemia anticancer)	Induce apoptosis, arrest cell cycle, reduce proliferation, modulate oxidative stress and immune responses
Immunomodulation [138]	*Tribonema* sp. (macrophage activation), *Porphyridium* sp. (cytokine regulation), *Spirulina platensis* (anti-inflammatory immune boost)	Stimulate macrophages, regulate cytokine release, enhance innate/adaptive immune responses
Antidiabetic [143]	*Arthrospira platensis* (insulin-sensitizing), *Nannochloropsis oculata* (glucose-lowering)	Lower blood glucose, improve insulin sensitivity, regulate lipid metabolism and oxidative stress
Cardioprotection [144]	*Dunaliella salina* (hyperlipidemia prevention), *Tisochrysis lutea* (cardioprotective PUFAs), *Nannochloropsis* sp. (anti-inflammatory EPA)	Improve lipid profile, reduce oxidative stress, lower inflammatory markers, protect cardiac tissue

These compounds demonstrated potential for use in nutraceutical formulations and wound dressings, as well as bioactive additives in tissue-engineering scaffolds [141] and 3D bioprinting bioinks [145]. As mentioned in the previous section, microalgae assist in wastewater treatment by absorbing nitrates and phosphates from hospital effluents and producing hydrogen. The implementation of this capability through MES framework represents a sustainable integration of bioremediation of clinical wastes and synthesis of biomedical compounds from it. Moreover, microalgae such as *Chlorella vulgaris* and *Spirulina platensis* demonstrated the ability to adsorb and transport nanoparticles and quantum dots, suggesting their potential as natural delivery systems for nanoparticle-assisted cancer therapy [146].

In the context of BESs, cathodic metal ion reduction was explored primarily as a strategy for resource recovery and wastewater treatment, including hospital effluents containing metal contaminants [147]. In these systems, anodic microbial oxidation supplies electrons that drive electrochemically assisted metal reduction at the cathode, resulting in the formation of elemental metals or metal-containing precipitates under controlled conditions [148]. Several studies demonstrated the recovery of silver, gold [148], copper [149], phosphorus [150], iron oxides, and calcium–phosphate biominerals in BES configuration [151]. The biomedical relevance of these materials, such as antimicrobial activity [152], MRI and hyperthermia [153], or hydroxyapatite for bone grafts [154], was established largely in downstream characterization studies rather than during BES operation itself. The incorporation of microalgae in cathodic compartments further enabled metal uptake and accumulation within biomass, providing a complementary biological route for metal capture [155]. Collectively, these findings support the role of BESs as bioelectrochemical recovery and synthesis platforms, capable of producing metal-containing materials that may be

subsequently processed and evaluated for biomedical use, rather than as direct biomedical manufacturing systems.

In addition to biomineralization of valuable metals, MES extends their applications to the utilization of gaseous and carbon-based feedstocks. By applying an appropriate cathodic potential and supplying CO_2 (or bicarbonate), acetate and other short-chain organics are produced in cathodic compartment [156]. Acetate, in turn, can be biologically or chemically upgraded into polyhydroxyalkanoates (PHAs), bacterial nanocellulose, and acetyl-CoA–derived metabolites, which are precursors for biodegradable sutures, scaffolds, drug carriers, and regenerative matrices [157]. In addition, MES-driven reduction pathways offer the production of ethanol, butyrate, and other volatile fatty acids as intermediates in the synthesis of biopolymers and bioactive molecules [158]. Engineered acetogenic strains (such as *Sporomusa ovata*, *Clostridium ljungdahlii*) converted these carbon fluxes into high-value biomedical precursors, such as amino acids, organic acids, and biopolymers. Through this strategy, MES establishes a direct connection between carbon capture and the sustainable synthesis of biomedical polymers and therapeutic precursors [159]. Typically, the systems operate at cathodic potentials from −1.0 to −1.3 V relative to the standard hydrogen electrode, enabling efficient CO_2 reduction under conditions that minimize the progress of undesired competing reactions. Cathodic potential and inorganic carbon source critically influence biofilm formation in MESs. Applying −1.0 V versus Ag/AgCl under CO_2 pressure promoted the development of an *Acetobacterium*-rich biofilm, resulting in increased acetate and organic metabolite production. This biofilm demonstrated an enhancement in electron generation, reduction of ohmic overpotential, and intracellular hydrogen production. Optimization of operational parameters enhanced coulombic efficiency (approximately 69%) and overall system performance, enabling more efficient CO_2 conversion [160].

Although MES requires less energy than most thermochemical or fermentative acetate synthesis methods, it still experiences efficiency losses associated with biomass overgrowth, membrane resistance, and electron diversion [161]. Hybrid systems that combine in situ membrane extraction with ex situ sorption are therefore proposed as future designs, balancing yield, purity, and energy consumption. Such architectures are particularly relevant for biomedical manufacturing, where both high acetate purity and low contaminant load are essential for safe downstream conversion into therapeutic polymers and regenerative biomaterials [161].

The integration of bioenergy exploitation with simultaneous wastewater treatment positions this strategy as an efficient method for hydrogen generation with a minimal ecological footprint and cost-effective operation (~3.5 USD/kg H_2) [162]. MESs can be integrated with stacked MFCs to establish self-powered, circular platforms that simultaneously remediate hospital and industrial wastewater while driving the production of high-value materials through clinical wastewater treatment and CO_2 conversion. Fig. 5 presents a conceptual BES-based infrastructure proposed here as a sustainable platform for clinical systems, capable of simultaneous clinical wastewater treatment and conversion of captured CO_2 into therapeutically relevant biochemicals in a fully self-powered framework. The multiunit platform integrates algae-assisted MFC, MEC, and MES modules connected in series. Clinical wastewater is supplied to all units, including stacked MFCs, MECs, and MESs. The stacked MFCs generate the electrical power required to operate the downstream MEC and MES units, thereby enabling a self-sustained configuration. Consequently, clinical wastewater treatment and the generation of value-added products can be achieved without external electrical input. In addition to wastewater treatment, anodic biofilms formed across all BES modules promote EPS production, which holds potential pharmaceutical relevance. Algal growth in the cathodic chambers of the stacked MFCs further enhances treatment efficiency and enables the recovery of high-value metabolites, including algal biomass,

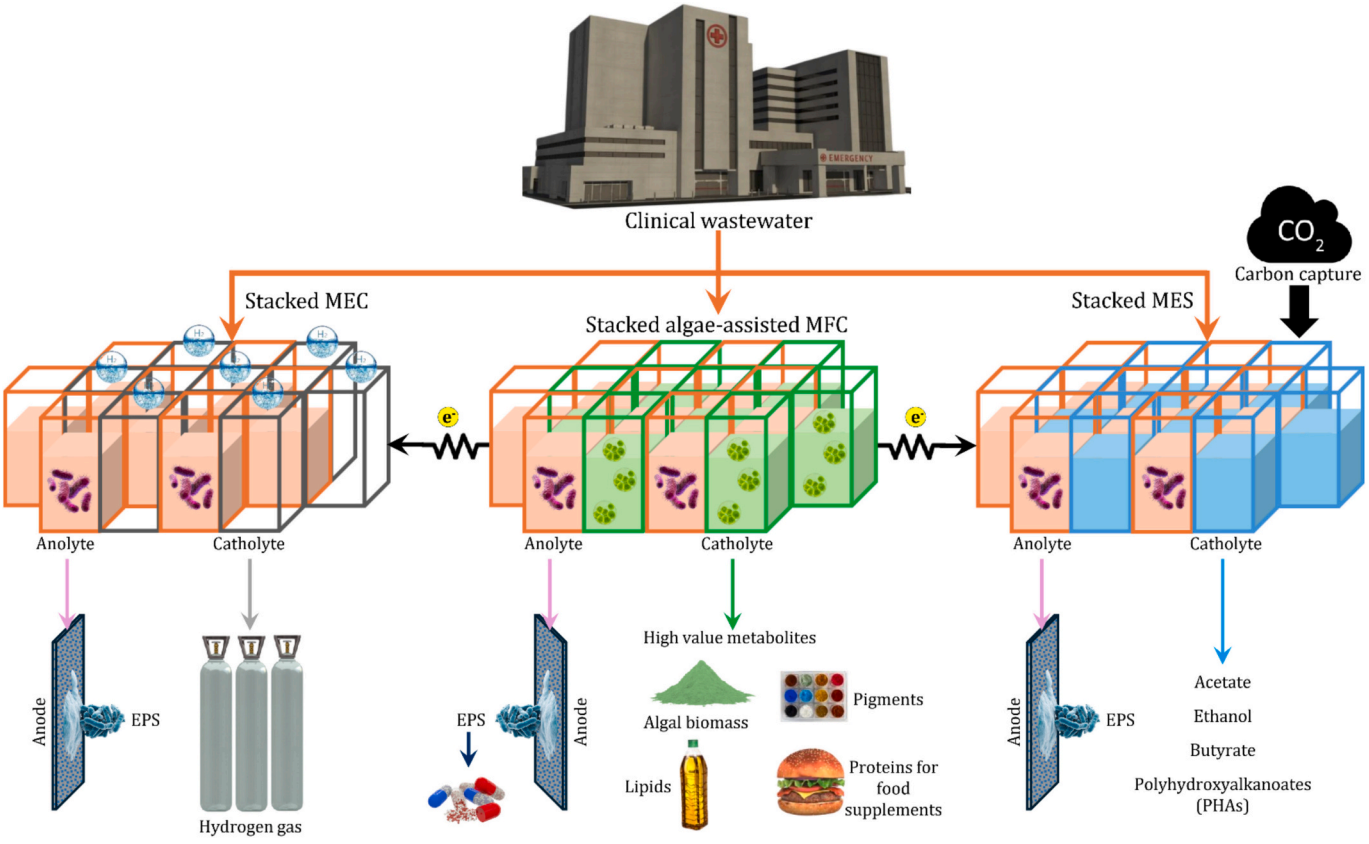

Fig. 5. Schematic representation of a multiunit BES platform for clinical wastewater treatment, consisting of algae-assisted MFC, MEC, and MES modules connected in series. In addition to clinical wastewater treatment, the platform enables the production of valuable biochemicals for therapeutic and pharmaceutical applications.

pigments, and lipids. Moreover, phosphorus and nitrate removal from clinical wastewater can occur within the cathodic compartments. The MEC units produce hydrogen gas for therapeutic applications, while the MES units function as carbon capture modules, converting CO_2 into valuable biochemicals such as acetate, ethanol, and butyrate. This configuration represents a conceptual sustainable infrastructure; validation through bench-scale studies, pilot-scale demonstrations, and further investigation remains necessary. This configuration can also be implemented in microstructured systems to support biomedical applications. For instance, smart wound adhesives in which sweat-fed bacteria provide metabolic energy to support algal growth, accelerating wound healing through local release of bioactives and oxygen, or self-powered MES devices that synthesize therapeutic compounds directly inside the body, offering a continuous, in situ drug supply.

From a medical translation perspective, the viability of MES depends on advances in product selectivity, downstream processing, and regulatory compliance, alongside clear benchmarking against conventional biomanufacturing methods. Product selectivity in MES is governed by biocatalyst composition [163,164], electron transfer pathways [165], and operational parameters [166], all of which influence suitability for medical applications. Pure acetogenic cultures can enhance selectivity toward defined compounds such as acetate, whereas mixed microbial consortia, although more robust, often activate competing pathways like methanogenesis unless rigorous inoculum pre-treatment is applied [167]. Cathode potential [168], cathode material [169], pH [170], and hydrogen-mediated electron transfer further regulate metabolic fluxes [167], yet these factors currently offer limited control over the selective biosynthesis of higher-value or medically relevant products. MES typically yields low product titers in dilute electrolytes, creating significant downstream processing challenges, particularly in the recovery and purification of organic acids from complex mixtures [171]. Achieving medical-grade purity requires additional separation steps to remove residual microorganisms, electrolytes, and electrode-derived contaminants, increasing process complexity and cost, and limiting translational feasibility [172]. Regulatory concerns also arise from the use of live microbial catalysts, evolving biofilms [173], and nanostructured or metal-containing electrodes [174], which impact process reproducibility, material stability, microbial containment, and compliance with good manufacturing practice standards. Compared with conventional biomanufacturing, which benefits from decades of metabolic optimization, high product titers, and established regulatory pathways [175], MES remains at an early stage of maturity. Nevertheless, ongoing advances in strain engineering, reactor design, and process integration could enable MES to evolve into a viable platform for producing medically relevant intermediates and specialty biochemicals, particularly in contexts emphasizing sustainability, decentralization, or on-demand manufacturing.

6. Bioelectrochemical approaches to biosensing and medical diagnostics

Through the metabolic activity of electroactive bacteria, BESs convert organic substrates into electrical signals that reflect analyte concentration, achieving real-time, label-free sensing performance [176]. Environmental and physiological variables such as pH, temperature, oxygen availability, inhibitory substances, and mechanical stress, affect microbial activity and thereby modulate electrical output, enabling the indirect detection of these parameters [177,178]. By combining direct substrate detection with responsiveness to environmental changes, BESs function as a multifunctional biosensing platform [179]. In addition to their established use for evaluating water quality through biochemical oxygen demand (BOD) measurements [180], MFCs hold significant potential for diagnostic applications. The fundamental mechanisms enabling microbial metabolism to produce detectable electrical currents in wastewater also apply to biological fluids and tissues [181]. BESs can monitor variations in metabolite concentrations such as glucose or lactate [182], detect toxins [84], and respond to physiological changes [178], which offer continuous, self-powered sensing in complex matrices such as blood [18], sweat [24], and wound exudate [21].

BESs exhibit enhanced durability, self-sustained energy functionality, and adaptability to intricate biological and environmental matrices. Their biological specificity and adaptability make them ideal for next-generation biosensing in healthcare and environmental applications [1]. BES-based biosensors can be classified according to their target analytes and electrochemical sensing mechanisms into four principal categories, with an additional category representing future potential, as outlined in Table 4. (1) Metabolic substrate sensing relies on the direct oxidation of organic compounds such as glucose, lactate, acetate, and urea, by electroactive bacteria, resulting in electron release to the anode and generation of electrical currents that scale quantitatively with analyte concentration. This mechanism enables real-time, self-powered monitoring of metabolic status in applications such as sepsis diagnosis, diabetes management, and wound exudate analysis [180]. (2) Toxic compound sensing exploits the inhibitory effects of xenobiotics, such as heavy metals, antibiotics, and phenolic compounds, on microbial metabolism and EET pathways. Suppression of bioelectrochemical activity leads to measurable reductions in current output, allowing assessment of drug toxicity, chemotherapeutic efficacy, and antimicrobial resistance [84]. (3) Environmental and physiological sensing is based on the sensitivity of biofilm viability, redox activity, and electron transport kinetics to parameters such as pH, temperature, salinity, dissolved oxygen, and electrolyte composition. Variations in these factors modulate BES performance and permit indirect sensing of physiological states, including wound healing progression, inflammatory status, and implant integrity [183]. (4) Pathogen detection and biological activity marker sensing depend on microbial community perturbations, metabolic shifts, or competitive substrate utilization induced by pathogenic organisms or infection-associated metabolites, enabling detection of infections, fecal contamination, and systemic sepsis [184]. For example, a 3D paper-based MFC leveraging the metabolic activity of *Pseudomonas aeruginosa*, combined with resazurin-mediated electron transfer, enabled rapid evaluation of antibiotic susceptibility across clinically relevant concentration ranges [185].

Beyond currently metabolized substrates, BES platforms also offer opportunities for next-generation biomedical sensing targeting biomolecules such as hormones, neurotransmitters, proteins, enzymes, immune effectors, and tumor-associated metabolites, which are relevant to stress assessment, neurological disorders, cardiovascular disease, cancer, and immune dysregulation. Although these targets are not intrinsically processed by electroactive bacteria, advances in synthetic biology, metabolic engineering, and genetic circuit design enable the development of engineered strains capable of signal transduction from molecular recognition events to electrical outputs [186]. Alternatively, hybrid BES–biosensor architectures integrate immunosensors, aptamers, or enzyme-based recognition layers with BES electrodes, combining high molecular specificity with self-powered electrochemical readout. For instance, electrons extracted by bacteria can be routed to a gold nanoparticle–modified cathode functionalized with single-stranded DNA probes. Target-induced hybridization then forms a double-stranded barrier that impedes electron transfer, reduces power output, and generates a quantifiable DNA detection signal [93].

Examples of some studies demonstrating the performance of MFC-based biosensors are illustrated in Fig. 6, highlighting the versatility of paper-based MFC platforms for biochemical sensing and on-demand power generation. Fig. 6 A presents a spore-forming whole-cell glucose sensor based on *Bacillus subtilis* spore germination, where selective germination in potassium-rich fluids induces metabolic activity proportional to glucose concentration, producing electrogenic signals within a paper-based MFC [182]. In this system, the anode is coated with PEDOT:PSS/dimethyl sulfoxide (DMSO) and 3-glycidyloxypropyl trimethoxysilane (3-GLYMO) to immobilize spores, while the cathode

Table 4
Classification of BES-based biosensors for biomedical applications: current analytes, detection principles, and future potential.

Category	Biomedical Applications	Target Analytes	Principle	Representative patterns of electrical signal changes
Organic content	Monitoring metabolic status, diabetes analysis [182]	Glucose, lactate, acetate, urea, COD (wound fluid, wastewater)	Oxidation of bioavailable organic substrates by electroactive bacteria produces electrons, resulting in a concentration-dependent electrochemical response within an operational range	Increase in current or power density within a defined range; signal saturation or plateau at high substrate concentrations
Toxic compounds	Drug toxicity, chemotherapeutic monitoring, heavy metal poisoning, antimicrobial resistance screening [185]	Heavy metals (Hg^{2+}, Pb^{2+}, Cd^{2+}), antibiotics, phenols, disinfectants	Toxic compounds inhibit microbial metabolism and/or extracellular electron transfer pathways	Decrease in current or power density; increased internal resistance; reduced charge-transfer kinetics
Environmental conditions	Wound healing, wearable health monitors, electrolyte balance, inflammatory status [21]	pH, temperature, salinity, dissolved oxygen, ionic strength of electrolytes (Na^{+}, K^{+}, Ca^{2+}, Cl^{-})	Environmental parameters modulate microbial activity, biofilm properties, and electron transport efficiency	Reversible baseline current drift; modulation of steady-state current; changes in impedance or open-circuit potential
Biological activity markers	Point-of-care infection detection, diagnostics and monitoring [187]	Pathogenic bacteria, wound infection markers, fecal contamination	Pathogens or their metabolites alter microbial community behavior, compete for substrates, or interfere with electron transfer	Irregular current fluctuations; delayed response; signal suppression or enhancement depending on microbial interaction
Future potential biomarkers	Broader biomedical diagnostics: stress, endocrine, neurological, cardiovascular, cancer	Hormones (cortisol, insulin, thyroid), neurotransmitters (dopamine, serotonin), proteins/enzymes, nitric oxide, tumor metabolites, Immune effectors (cytokines)	Detection beyond native microbial metabolism enabled by engineered strains, metabolic coupling, or BES–biosensor hybrid architectures	Analyte-specific current modulation, potential shifts, or impedance changes determined by engineered sensing pathways

incorporates Ag_2O in PEDOT:PSS with backside blocking to prevent crossover, achieving a high sensitivity of 2.246 $\mu W \cdot (\log mM)^{-1} \cdot cm^{-2}$ across physiologically relevant glucose concentrations (0.2–10 mM) and a low detection limit of ~0.07 mM [188]. Extending this concept toward self-powered diagnostics, Fig. 6B shows a saliva-activated paper-based MFC that functions both as a micropower source for point-of-care devices and as a glucose biosensor, in which *Pseudomonas aeruginosa* generates electrical power within minutes after rehydration with a single drop of saliva, with sixteen MFCs connected in series providing sufficient energy to power an LED and electrical outputs scaling across glucose concentrations of 0–19.4 $mg \cdot dL^{-1}$. Beyond glucose sensing, Fig. 6C demonstrates the applicability of paper-based MFCs for environmental monitoring, depicting a single-component, metal-free MFC biosensor for water quality assessment that exhibits a rapid current decrease upon exposure to 0.1% *v*/v formaldehyde, reaching ~95% of the steady-state response within 165 min while retaining scalability through folding and stacking configurations [189].

BES-based biosensors can function as wearable depending on the analyte and sample type [190]. *E*-textiles [23,191], microneedle patches [94], and smart dressings [21] monitor organic substrates such as glucose, lactate, and urea in sweat, saliva, tears, and wound exudate. The detection of toxic compounds like heavy metals and antibiotics require microneedle-based systems for continuous monitoring in blood or interstitial fluid [192]. Flexible patches or bandages provide suitable platforms for monitoring environmental parameters such as pH, temperature, electrolytes, and oxygen. Detecting pathogens in wound exudate, saliva, or fecal samples necessitates the use of biocompatible biosensing systems. Future detection of complex analytes such as hormones, neurotransmitters, proteins, and immune metabolites demands the design of advanced or hybrid BES architectures to achieve enhanced diagnostic performance.

Although a few BES-based biosensors for biomedical applications have been reported, key performance metrics such as detection limit, linear range, response time, and stability are often incompletely reported. A comparative summary of available metrics is provided in Table S1, supplementary materials. This highlights current gaps and emphasizes the need for systematic studies to develop BES-based biosensors with improved performance, stability, and practical applicability.

A key challenge for BES-based biosensors is selectivity, as electroactive bacteria oxidize many organics, making analyte-specific responses difficult. This can be improved through metabolic engineering or selecting elements that capture specific analytes such as enzymes and molecularly imprinted polymers [193]. Sensitivity is another limitation since current output may not linearly reflect analyte concentration, requiring optimization of electrodes, cell design, and electron transfer. Biosafety concerns arise because some efficient electroactive bacteria are pathogenic, necessitating safer or engineered non-pathogenic strains. For biomedical applications, issues include biocompatibility, stable biofilm formation, and sustained electron acceptor supply. Developing flexible, non-toxic materials and controlled biofilm growth strategies is crucial for reliable, long-term operation in physiological environments.

7. Bio-safety assessment and containment strategies for healthcare BES

The transition of BESs from benchtop prototypes to clinical applications necessitates a rigorous evaluation of the clinical safety of the devices, focusing on infection prevention, immunotoxicity, and containment reliability. To ensure device safety, biosafety assessment must proceed across three interconnected levels: (i) intrinsic biological risk associated with the selected microbial chassis, (ii) physical and genetic containment strategies that prevent unintended exposure or dissemination, and (iii) sterilization protocols and regulatory oversight governing device manufacture and deployment. These tiers collectively define the translational feasibility of healthcare BESs.

7.1. Strain selection and immunotoxicity risk

The primary safety consideration involves the selection of biological agents. Early biomedical MFCs frequently employed *Pseudomonas aeruginosa* due to its efficient endogenous mediator production [7]; however, its classification as an opportunistic pathogen (Risk Group 2) renders it unsuitable for clinical applications, particularly in immunocompromised patients [194]. Consequently, current research emphasizes Risk Group 1 (RG1) organisms with generally recognized as safe (GRAS) status, such as *Bacillus subtilis* and *Saccharomyces cerevisiae* [195]. Notably, even non-pathogenic Gram-negative bacteria (e.g., *Shewanella oneidensis*) pose immunological concerns owing to

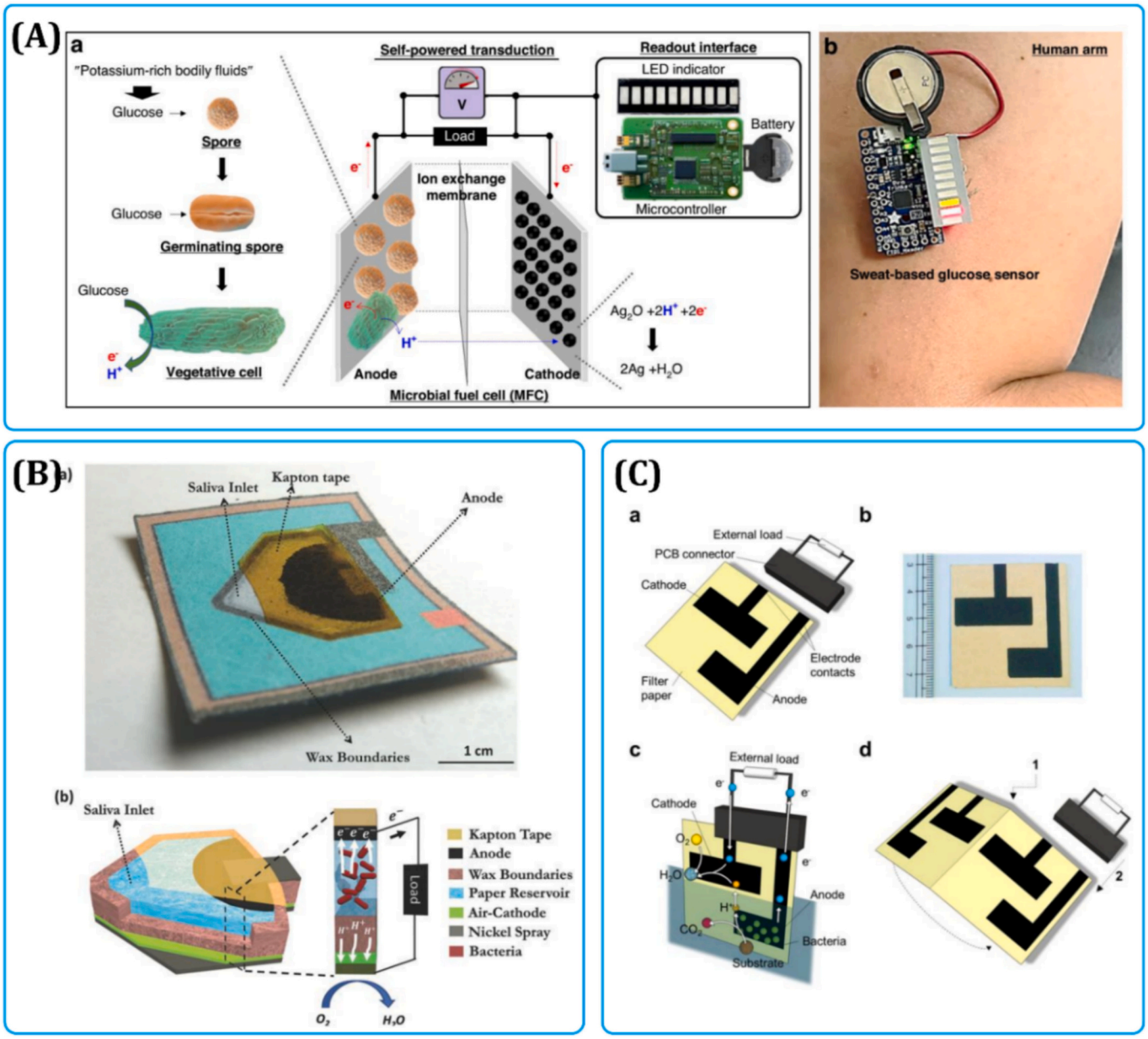

Fig. 6. (A) a spore-based *Bacillus subtilis* MFC enabling self-powered glucose detection (0.2–10 mM) with high sensitivity (~0.07 mM). Reproduced with permission from [182]. (B) a saliva-activated MFC using *Pseudomonas aeruginosa* generating power responsive to 0–19.4 mg·dL^{-1} glucose. Reproduced with permission from [188]. (C) a single-component, metal-free MFC rapidly detecting 0.1% v/v formaldehyde, reaching 95% steady-state current within 165 min. Reproduced with permission from [189].

lipopolysaccharides (LPS) in their outer membranes, which act as endotoxins and may elicit strong inflammatory responses upon systemic exposure [196,197]. Therefore, for bioelectronic applications, Gram-positive strains or engineered probiotic chassis (e.g., *Lactococcus lactis* [198], *Escherichia coli* Nissle 1917 [199]) are often preferred to reduce endotoxin-mediated immunotoxicity.

7.2. Physical and biological containment strategies

To prevent bacterial leakage and subsequent infection, a "multi-layer defense" strategy is required. Physical containment relies on semi-permeable membranes with nanoscale pore sizes that permit the diffusion of metabolites like glucose, lactate and ions while strictly retaining bacterial cells [200]. Encapsulation techniques, such as trapping bacteria within alginate-silica or polyvinyl alcohol (PVA) hydrogels, provide a secondary physical barrier that prevents cell escape even if the outer membrane is compromised [201]. Furthermore, "biological containment" via synthetic biology offers a failsafe mechanism. This includes the engineering of auxotrophic strains that cannot survive without specific non-biological supplements, or the integration of genetic "kill switches" that trigger cell lysis if the bacteria escape the specific microenvironment of the device [202].

7.3. Sterilization and regulatory supervision

Clinical medical devices must adhere to stringent sterility and biocompatibility requirements, including compliance with standards governing bioburden control, sterilization validation, and biological safety (e.g., ISO 11737 [203] and ISO 10993 [204]). This creates a "sterilization paradox" for BESs: conventional terminal sterilization methods (e.g., autoclaving, ethylene oxide, or irradiation) required for the device housing would irreversibly damage the active anodic biofilm.

To address this, aseptic manufacturing and fill/finish workflows should be implemented, ensuring that the biological component is maintained under controlled sterile conditions and integrated into the device housing only at the point of assembly or activation, with sensitive materials potentially stabilized prior to aseptic incorporation [205]. Regulatory supervision must also address genetic safety risks, including horizontal gene transfer (HGT), particularly when antibiotic resistance genes are used as selectable markers in engineered strains [206]. The removal of such markers is widely expected for clinical applications, as it reduces the risk of resistance dissemination within the host microbiome and aligns with current regulatory guidance for live biotherapeutic and genetically modified products [207].

8. Engineering and integration aspects of BESs

Engineering approaches in BES development focus on four principal goals: maximizing bioenergy output, maintaining biocompatibility, ensuring durable stability, and optimizing overall cost-effectiveness. This section addresses essential parameters governing these objectives, from the modification of microbial metabolism and the assurance of its non-pathogenicity to the engineering of electrodes, catalysts, and membranes that facilitate electron transfer between electron donors and final electron acceptors. In addition, the development of suitable devices for biomedical applications requires the integration of biocompatible materials, microfabrication techniques, and electronic interfaces.

8.1. Bioengineering of electroactive bacteria for biomedical BESs

The use of non-pathogenic electroactive microorganisms is a vital requirement to ensure the safety and reliability of BESs in biomedical environments. Due to their reliable extracellular electron transfer abilities and non-pathogenic profiles, *Geobacter sulfurreducens* and *Bacillus subtilis* are most commonly employed, whereas organisms such as *Shewanella oneidensis*, *Pseudomonas aeruginosa*, and *Escherichia coli* require strict biosafety evaluation and genetic modification [11,208]. Genetic modifications, such as overexpression of *mtrCAB* and *omcZ*, enhance extracellular electron transfer efficiency, biofilm growth in stressful environment (characterized by fluctuating conditions such as pH, temperature, etc.), and improving performance in complex fluids such as sweat or serum [87].

Synthetic biology provides a framework for creating self-sustaining systems, such as those in which *Shewanella* utilizes lactate secreted from tumors to generate electricity that induces targeted drug release and counteracts resistance to chemotherapy [209]. In the context of BES-based biosensing, genetically modified strains can improve both the precision and responsiveness of biosensors for diagnostic purposes.

The stability of BESs and electroactive bacteria is strongly influenced by dynamic physiological and operational conditions that challenge both biofilm integrity and electrochemical performance. In continuously fed systems, anolyte flow imposes shear stresses that disrupt biofilm adhesion, alter mass transport, and cause partial detachment of weakly attached electroactive communities [210]. In both batch and continuous operation, physiological pH fluctuations associated with inflammation, ischemia, or host metabolism [211], together with local pH gradients generated by bacterial metabolism and substrate oxidation at the electrode interface [212], and variations in nutrient availability [213], can modulate microbial respiration pathways and electron transfer kinetics, leading to current drift or reduced power output [214]. Long-term operation is further compromised by biofouling on cathode and membrane surfaces, driven by microbial colonization, metabolite accumulation, and physicochemical interactions, which impair proton transfer and oxygen reduction. In future BES prototypes, rapid adsorption of host plasma proteins onto electrode surfaces initiates foreign body responses that can electrically isolate the device and restrict substrate diffusion [215,216]. Addressing these challenges requires antifouling surface engineering, modular electrode designs, controlled local environments, and enhanced bacterial stress tolerance through genetic engineering.

8.2. Engineering of electrodes, catalyst and proton exchange membrane

Electrode architecture is critical for BES performance, affecting electron transfer, the growth of electroactive biofilms, and consequently the rate of bioenergy generation. The combination of nanostructured materials [217], metal–organic frameworks (MOFs) [218], and MXene composites [219] significantly enhances the conductivity and availability of active sites in carbon-based electrodes such as graphite felt and carbon cloth [60]. These modifications support dense bacterial colonization, strengthen biofilm–electrode interactions, and shorten electron pathways, enhancing electrochemical activity and stability [91]. Metal-based electrodes demonstrated outstanding performance due to their high electrochemical potentials [57]. Surface functionalization and utilization of conductive polymers (PEDOT:PSS, polyaniline, polypyrrole) create soft, hydrophilic interfaces promoting bacterial attachment and biofilm growth and decrease ohmic overpotential [61]. Additionally, the combination of PEDOT:PSS with nanomaterials and metal oxides enhances conductivity, expands active sites and improves charge transfer which eventually promotes the stability and efficiency of energy generation [220]. These hybrid materials that integrate conductive polymers with nanoparticle additives exhibit high flexibility, enhanced conductivity, and excellent biocompatibility, making them suitable as the main structural components of wearable MFCs.

Natural polymer matrices, for example those composed of alginate or agar, enhance biofilm development and enable up to twofold power density improvement while retaining biocompatibility [221]. In the context of sustainable material utilization for BESs, carbon-rich algal biomass can be processed into heteroatom-doped porous carbon anodes with high conductivity and surface area, enhancing charge transfer efficiency in biomedical MFCs, which have also demonstrated potential for Li-ion batteries and other energy storage devices [222]. The combination of living algae with conductive polymers, such as polyurethane (PU) and PEDOT:PSS, enhanced both redox activity and biocompatibility and was demonstrated effectively in *Lobochlamys segnis*–based anodes [223]. Algae also act as natural templates for metal-composite bioanodes. For instance, *Spirulina platensis* adsorbed tin ions and produced Sn@C porous structures containing uniformly distributed nanoparticles, which improved electrochemical performance for in vivo applications [224]. Integrating algal carbon with metal composites [225], SiO_2/C [226], or $Ni(OH)_2$ nanocomposites [227] enhances conductivity, structural stability, mechanical strength, and ion/electron transport, collectively boosting the performance of bioanodes.

The catalyst layer of the cathode is a critical component for oxygen reduction and has a major impact on the efficiency and cost of BESs. For practical biomedical deployment, catalysts must exhibit activity at physiological temperature and pH while maintaining chemical and mechanical integrity and adhering to the four-electron oxygen reduction pathway in complex biological environments. Despite the outstanding catalytic performance of platinum, its high cost, scarcity, and susceptibility to poisoning in physiological media restrict its role in biomedical technologies. Non-precious and carbon-based catalysts were reported as promising alternatives due to their strong catalytic activity, stability, and biocompatibility [228]. Carbon nanotubes (CNTs) [229] and carbon nanofibers (CNFs) [230] display high performance in oxygen reduction, with additional improvement achievable through heteroatom doping, surface modification, or incorporation of transition metal oxides such as MnO_2, MoS_2, or CuO/ZnO [231]. Incorporating Fe, Co, or N to form M–N–C active sites improves catalytic efficiency while ensuring safety [232].

The membrane is another critical component of BESs, requiring high proton conductivity, selective ion transport, minimal oxygen and substrate crossover, stability, and biocompatibility. Though Nafion ensures exceptional proton conductivity, its unsustainable nature, high cost, and proneness to poisoning restrict its adoption in advanced electrochemical

applications [233]. Alternatives, including sulfonated PEEK, polysulfone, polypropylene, and chitosan-based membranes, support microbial growth while maintaining selectivity. Nanocomposite membranes with uniformly distributed nanoparticles improved water affinity, proton conduction, and effective surface exposure, resulting in higher MFC performance, stability, and suitability for biomedical applications [234].

8.3. Fabrication of biocompatible BESs

The advancement of BES technologies for biomedical applications highly depends on the deliberate incorporation of electrochemical elements into material frameworks capable of maintaining tissue and environmental compatibility [22]. Table 5 summarizes the major classes of conductive and stretchable materials used in bioelectronic systems for biomedical applications, highlighting the trade-offs between electrical performance, mechanical compliance, and practical integration. Conventional metals such as gold, zinc, copper, and aluminum exhibit very high electrical conductivity and compatibility with electroactive biofilm [57] and also established advanced printing techniques [235], making them reliable choices for electrodes and interconnects. However, their intrinsic rigidity and low stretchability limit their use in deformable or skin-mounted systems unless complex structural designs are introduced to accommodate strain. Metal nanostructures and metal–polymer composites address some of these limitations by enabling tunable conductivity and stretchability through control of filler concentration and composite architecture [27]. These materials are well suited for printable conductive traces and strain sensors, although their long-term reliability can be compromised by junction resistance, oxidation, and percolation breakdown under repeated mechanical deformation. Liquid metals, including EGaIn and Galinstan, offer an extreme level of stretchability and self-healing behavior while maintaining high conductivity, making them attractive for soft wiring and microfluidic-based circuits. Their broader adoption is constrained by leakage risks, patterning challenges due to high surface tension, and the cost of liquid metals-based alloys [236]. Conductive polymers such as PEDOT:PSS, polyaniline, and polypyrrole provide a balance between flexibility, biocompatibility, and electrical functionality, supporting their use in soft electrodes, sensors, and energy-storage components, despite moderate conductivity and susceptibility to mechanical fatigue [61]. Carbon-based materials, including carbon nanotubes and graphene, offer lightweight, chemically stable, and transparent conductors, but issues related to brittleness, dispersion, and scalable fabrication remain [237]. Hybrid materials that combine metals or carbon fillers with elastomeric polymers represent a promising route toward fully stretchable and durable bioelectronics, while soft substrate and encapsulation polymers provide the mechanical compliance and biocompatibility required for intimate tissue and skin interfacing, despite being electrically insulating [238]. Soft polymeric substrates, such as PDMS and hydrogels, provide compliance and biocompatibility but are electrically insulating making them suitable only for BES regions where electrical conductivity is not required [26]. Overall, the careful selection and integration of conductive and compliant materials is critical to balancing electrical performance, mechanical flexibility, and biocompatibility in biomedical BESs, guiding the design of robust, tissue-compatible bioelectronic systems.

Table 5
Overview of conductive and stretchable materials used in bioelectronic systems for biomedical applications.

Material class	Key Features / Advantages	Limitations / Challenges	Typical Applications
Metals (Au, Zn, Cu, Al) [57]	- High electrical conductivity (>10^5 S/cm) - Compatible with lithography and printing - Stable, reliable interconnects	- Rigid and brittle - Low stretchability (<5%) - Requires patterning to tolerate strain	Interconnects, electrodes
Metal Nanostructures & Composites (Ag and Cu nanoparticles) [27]	- Tunable conductivity/ stretchability via filler content - Printable and scalable fabrication - Resistant to fatigue	- Junction resistance - Oxidation and percolation failure under strain	Conductive traces, strain sensors
Liquid Metals (EGaIn, Galinstan) [239]	- Soft, self-healing - Extremely stretchable (>1000%) - High conductivity (~10^6 S/m)	- Leakage risk - High surface tension, difficult patterning - Expensive alloys	Microfluidic circuits, stretchable wiring, sensors
Conductive polymer (PEDOT:PSS, PANI, PPy) [61]	- Flexible and biocompatible - Printable - Tunable via chemical doping	- Moderate conductivity (10^2–10^4 S/cm) - Prone to mechanical fatigue - Some dopants are cytotoxic	Electrodes, soft interconnects, sensors, supercapacitors
Carbon-Based Materials (CNTs, Graphene) [237]	- Lightweight, chemically stable, transparent - High aspect ratio enables conductive percolation - Biocompatible	- Brittle under strain - Alignment and dispersion difficulties - Complex fabrication	Transducers, strain-insensitive wiring, transparent circuits
Hybrid / Composite Materials (metal–polymer, carbon–polymer) [238]	- Combine conductivity of metals with elasticity of polymers - Self-healing and durable - Tunable electrical/ mechanical properties	- Interfacial mismatch - Processing complexity	Fully stretchable circuits, wearable sensors
Substrate / Encapsulation Polymers (PDMS, Ecoflex, hydrogels, silk fibroin) [26]	- Soft, elastic, biocompatible, breathable - Skin-conformal - Transparent or semi-transparent	- Electrically insulating - Potential delamination at interfaces	Skin-contact layers, protective encapsulation, flexible supports

8.4. Integration with electronics and biomedical systems

Integrating BESs with electronic and biomedical platforms allows their use as self- or hybrid-powered devices for sensing, actuation, and therapy. Effective integration requires power management circuits to regulate the inherently low and variable microbial outputs through voltage control, impedance matching, and energy buffering with micro-supercapacitors or thin-film batteries [240]. Such circuits are essential to ensure stable operation of downstream electronics and to accommodate fluctuations in metabolic activity. In parallel, low-power signal conditioning, amplification, and analog-to-digital conversion modules are needed to translate bioelectrochemical signals into reliable physiological readouts [241]. Wireless communication interfaces, such as Bluetooth Low Energy and near-field communication, allow real-time data transmission and intermittent power support without tethering, provided that ultra-low power consumption and stable regulated supply voltages are maintained [242]. Beyond sensing, BESs can be incorporated into closed-loop biomedical architectures in which microbial electrical signals dynamically modulate therapeutic responses, such as controlled drug release [243], electrical stimulation for tissue regeneration, or modulation of local biochemical environments [244]. The

integration of these components is a fundamental requirement for BES platforms to transition from proof-of-concept systems to valuable and deployable biomedical devices.

8.5. Emerging biohybrid and microrobotic applications

Integrating bacterial motility, electron transfer, and engineered sensing enables autonomous microsystems for confined or dynamic physiological environments. Electroactive bacteria act as living actuators in soft robotic systems, providing adaptive, self-sustained operation. Their diverse modalities, such as magnetotaxis (*Magnetospirillum magneticum* [245]), electrotaxis/galvanotaxis (*E. coli*, *B. subtilis* [246]), chemotaxis (*P. aeruginosa* [247]), phototaxis (cyanobacteria [248]), and thermotaxis (*E. coli* [249]), allow targeted navigation along biochemical gradients. When combined with microfabricated carriers, surface functionalization, and programmable external fields, these taxis mechanisms enable spatiotemporal control, collective behavior, and task-specific deployment in complex physiological environments [250,251]. Extending beyond locomotion, these biohybrid microrobots engage in various therapeutic operations such as targeted pharmacological release, oxidative stress control, localized monitoring, and electrical stimulation aiding tissue regeneration. Electroactive bacteria driven biohybrids represent the emergence of a new generation of self-powered, adaptive soft robots designed for sophisticated biomedical functions [31,32].

A micro-nano microbial fuel cell (MnO_2 nanoparticle shell modified with norepinephrine (NE) and polyethylene glycol (PEG)) encapsulated *Desulfovibrio desulfuricans*, enabling lactate oxidation at the bioanode while MnO_2 catalysis generated reactive oxygen species (ROS) and Mn^{2+}, promoting tumor destruction through oxidative stress and metabolic disruption. The NE–PEG layer enhanced bacterial adhesion, mucus penetration, and stability, allowing oral administration and targeted colonization of the tumor microenvironment. Mechanistically, this system induced Ca^{2+} overload, membrane depolarization, and a switch from apoptosis to pyroptosis, an immunogenic form of cell death that promotes tumor antigen release and immune activation. Additionally, bioelectrochemical interactions between *D. desulfuricans* and MnO_2 modulate local metabolic and immune pathways, enhancing dendritic cell activation, macrophage polarization, and T cell infiltration, highlighting the potential of self-powered microbial–inorganic hybrids as adaptive, tumor-targeted therapeutic platforms [31].

Similarly, *Shewanella oneidensis* MR-1 used tumor lactate as an electron donor and MnO_2 nanoflowers as an electron acceptor, establishing a self-sustained bacterial respiration pathway at the tumor site. This biohybrid device continuously oxidized intercellular lactate, depleting a metabolite essential for tumor growth, while MnO_2 catalyzed the conversion of endogenous H_2O_2 into O_2, alleviating hypoxia and downregulating HIF-1α. Coupling bacterial respiration with tumor metabolism effectively inhibited tumor progression. Hypoxia-guided chemotaxis enhanced tumor targeting, ensuring localized activity, while bioelectrochemical interactions provided a self-powered, adaptive mechanism for therapy. Together, lactate depletion, oxygen generation, hypoxia relief, and precise tumor localization highlight the potential of this biohybrid microrobotic platform for metabolic and immunomodulatory cancer interventions [32].

9. Conclusion and future directions

Integrating BES functionality into healthcare technology frameworks is driving the development of sustainable devices capable of generating electricity while performing biosensing, producing valuable biomedical compounds, and executing targeted therapeutic tasks. Future studies in this domain should center on versatile and biocompatible architectures capable of utilizing these functionalities. Interdisciplinary collaboration and standardized testing protocols are essential to enable the clinical translation of these technologies.

The first promising direction is the development of clinical waste infrastructure based on self-powered BESs that support on-site waste-to-energy conversion for medical or laboratory use. MFC stacks generate power to drive MECs and MESs for hydrogen production and the synthesis of high-value materials, respectively. This sequence of BESs supports the production of therapeutic hydrogen and valuable biomedical compounds, as well as bioremediation. Such hybrid, self-powered systems simultaneously treat hospital effluents while generating useful bioenergy. Incorporating photosynthetic algae into the cathodic compartments also provides carbon dioxide capture and oxygen generation, creating a self-sustaining redox environment. Pilot studies in real clinical settings could validate energy output and bioremediation efficiency under variable conditions.

Parallel to system-level integration, genetic engineering of electroactive bacteria will be essential to improve performance and safety of BESs. Enhancing bacterial electron transfer through overexpression of elements such as cytochromes, conductive pili, or redox enzymes offers a promising route to boost bioenergy generation. In addition, genome-editing approaches can reduce pathogenicity, advancing the safe implementation of invasive BES platforms. For biosensing applications, synthetic biology tools can program bacteria to respond selectively to target analytes by connecting metabolic recognition mechanisms to clearly detectable electrical outputs. Enhanced microbial robustness will also be crucial to ensure stable function in tissue-like or physiological environments, enabling long-term operation in biomedical contexts. Developing standardized testing models for tissue-like conditions could provide reliable benchmarks for bacterial performance and safety. Interdisciplinary efforts integrating microbiology, synthetic biology, and biomedical engineering will be critical to ensure safe and effective translation.

The development of eco-friendly materials like conductive polymers, hydrogels, and natural composites in fabrication of wearable configurations of BESs is essential. Advances in microfabrication, microneedle arrays, and textile integration technologies will facilitate the creation of wearable BESs capable of extracting bioenergy from natural secretions such as sweat, tears, and interstitial fluid. Moreover, biofabrication and additive manufacturing can support the creation of porous, low-resistance electrode scaffolds that promote bacterial colonization and efficient electron transport, further improving device output and stability. Establishing standards for materials and testing protocols will help ensure reproducibility and safety for long-term wearable applications.

Advancing toward clinical translation requires preclinical and stringent safety evaluation of BESs. Work in this direction should involve evaluating long-term bioenergy performance in biological environments and demonstrating therapeutic effects like in situ hydrogen release for antioxidant activity or electrochemical biomarker detection. Moreover, detailed investigations into biocompatibility, immunogenicity, and device safety are essential to validate successful tissue incorporation and mutual compatibility with IMDs.

Finally, hybrid BESs represent an emerging direction in BES research. The combination of microbial biocatalytic systems with nanomaterials, aptamer frameworks, or enzyme-driven electrocatalysts might offer substantial improvement in selectivity and sensitivity for the detection of clinically relevant analytes such as hormones, proteins, cytokines, and tumor-associated metabolites. Extending this concept, biohybrid microrobots powered or guided by electroactive bacteria may navigate within vascular systems for targeted therapy, thrombosis removal, or tumor ablation, representing a remarkable integration of bioelectrochemistry, robotics, and medicine. Strong collaborations between microbiologists, materials scientists, roboticists, and medical clinicians will be essential to develop functional biohybrid prototypes capable of safe and effective operation in vivo.

CRediT authorship contribution statement

Mohammad Mahdi Mardanpour: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Atieh Sadat Sadat Kachooei:** Writing – original draft, Investigation, Conceptualization. **Yan Yan Shery Huang:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Dan V. Nicolau:** Writing – review & editing, Validation, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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ChatGPT was used during manuscript preparation to assist in identifying and correcting grammatical errors, with final revisions ensuring accuracy and clarity. All scientific content, results, and interpretations are the sole responsibility of the authors.

Appendix A. Supplementary data

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Data availability

No data was used for the research described in the article.

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