

Recent Advances in Glucose Fuel Cells for Biomedical Applications

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Glucose fuel cells (GFCs), which convert glucose-derived bioenergy into electrical energy, have received significant attention for their potential applications in biomedical fields. Their inherent sustainability and potential for integration into devices make them particularly attractive for next-generation bioelectronics, especially in monitoring and therapeutic systems. In recent years, notable progress has been made in improving GFC performance, adaptability, and integration with physiological environments. This review summarizes recent advancements in GFCs, with a focus on catalyst and electrode structures, utilization of physiological glucose sources, and their advantages and limitations. It also highlights the biomedical applications of GFCs, including tissue repair, biosensing, drug delivery, and power supply. Finally, the key challenges, current limitations, and future directions for the clinical translation of GFC technologies are discussed. This review aims to serve as a valuable reference for the continued development of self-sustained, bioenergy-driven medical technologies.

support implantable and wearable medical devices. Devices such as pacemakers,^[1] insulin pumps,^[2] and emerging brain-computer interfaces,^[3] rely on highly integrated power systems to enable continuous monitoring and therapeutic functions. Among the various power solutions, glucose fuel cells (GFCs) have garnered growing attention due to their unique ability to convert endogenous biochemical energy into electricity, offering distinct advantages for long-term biomedical applications.

GFCs use glucose present in human body fluids as a fuel source. Fluids such as blood, interstitial fluid, saliva, and tears typically contain stable concentrations of glucose, providing a natural and sustainable basis for

continuous power generation. This widely available internal fuel source enables GFCs to directly generate electricity through the electrocatalytic oxidation of glucose, without the need for external energy storage, making them ideal for powering various implantable and wearable medical devices. Its theoretical energy density (4430.0 Wh kg⁻¹) is close to that of methanol (6100.0 Wh kg⁻¹),^[4] making it a clean fuel with a high energy density. This characteristic renders GFCs particularly promising for a range of biomedical applications, including tissue repair, biosensing, and drug delivery.

The energy conversion in GFCs takes place under mild physiological conditions, typically facilitated by catalysts, such as enzymes or noble metals. This process mitigates the risk of thermal damage and avoids the generation of byproducts like CO₂, distinguishing GFCs from traditional high-temperature fuel cells. Compared to conventional implantable batteries, such as Li-I₂ batteries^[5,6]—which are already highly miniaturized and capable of operating in vivo for over a decade—GFCs offer distinct advantages in sustainable energy supply. By continuously harvesting glucose from physiological fluids, GFCs can potentially overcome the intrinsic limitations of finite energy storage, enabling long-term operation without the need for replacement or external charging. Moreover, GFCs can be fabricated from biodegradable materials, allowing for the development of fully resorbable power systems that naturally degrade after completing their therapeutic function. In contrast, conventional batteries typically require surgical removal, posing risks of secondary injury and additional clinical burden.

GFCs offer significant advantages over other bioenergy harvesting technologies. Thermoelectric generators require substantial and stable temperature gradients, but maintaining the

1. Introduction

The rapid growth of the biomedical industry has created an urgent need for safe, stable, and miniaturized power sources to

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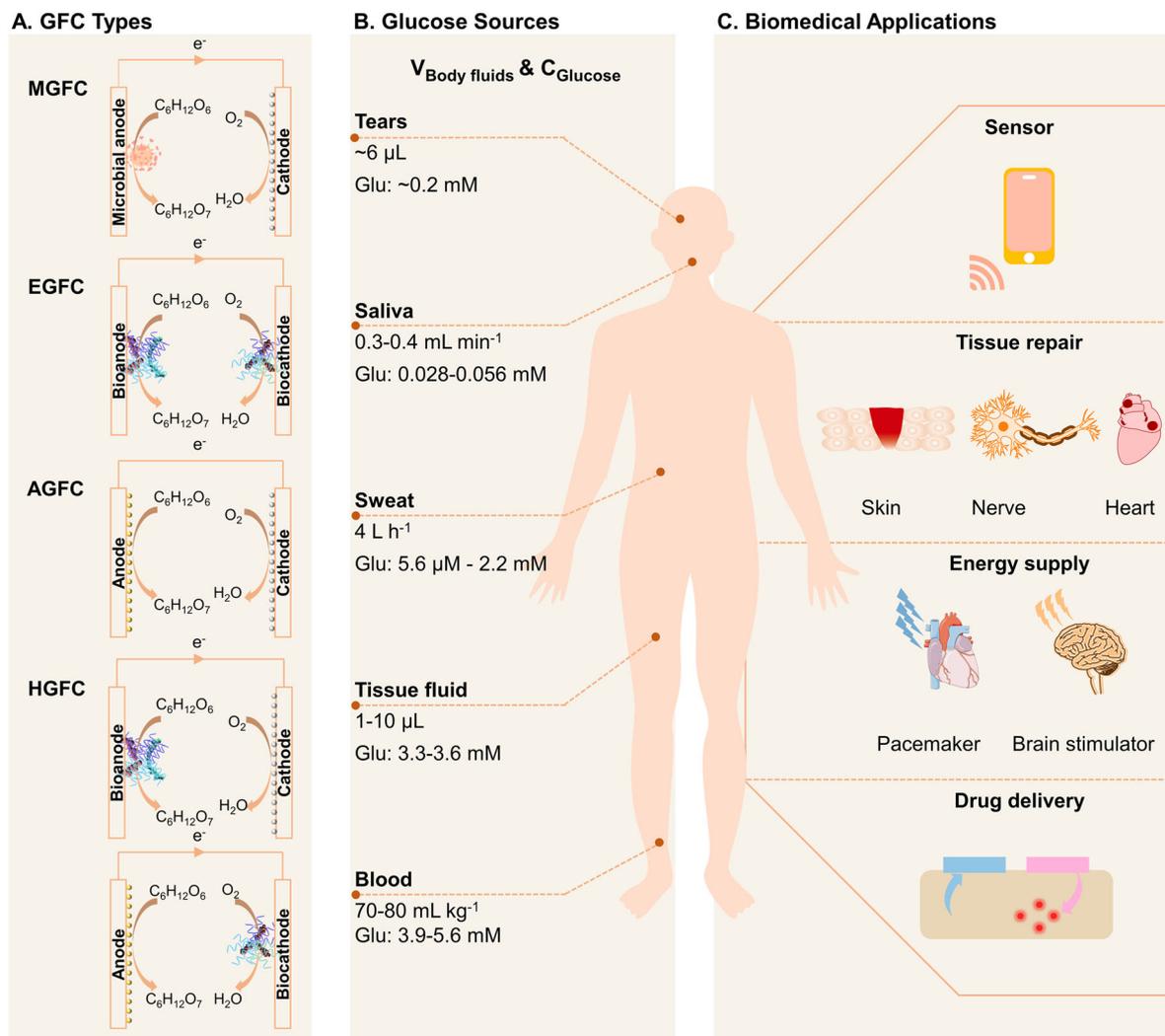


Figure 1. GFCs types, physiologic glucose sources, and biomedical applications.

necessary temperature difference in vivo is challenging. Piezoelectric and friction nanogenerators rely on cyclic mechanical motion, limiting their applicability to specific moving organs or body parts. In contrast, glucose fuel cells have demonstrated breakthrough advantages in terms of stability, sustained energy supply, environmental adaptability, and biocompatibility through the bioenergy-to-electricity conversion pathway. These advantages make GFCs an ideal solution for next-generation implantable medical device power supply systems.

This paper provides a comprehensive overview of recent advancements in the field of GFCs. Based on differences in catalyst types and electrode structures, GFCs are classified into microbial glucose fuel cell (MGFCs), enzymatic glucose fuel cell (EGFCs), abiotic-catalyzed glucose fuel cells (AGFCs), and hybrid glucose fuel cells (HGFCs) (Figure 1A). Each type is examined in terms of its working mechanism, technological advantages, and primary application scenarios, with key research cases providing clarification of their technological features. Additionally, the physiological sources of glucose (e.g., tears,^[7,8] saliva,^[9,10] sweat,^[11] tissue fluids,^[12,13] blood^[14]) are also examined for their accessibility and

suitability for energy harvesting (Figure 1B). The biomedical applications of glucose fuel cells are further summarized, highlighting their roles in areas such as biosensing, tissue repair, and drug delivery (Figure 1C). Finally, the challenges and future development trends of GFCs are discussed with respect to performance, characterization, and applications, aiming to offer valuable insights for future research in this field.

2. Working Principle and Types of GFCs

2.1. Developmental Milestones of GFCs

As a cutting-edge technology that converts glucose into energy, GFCs have undergone significant development and breakthroughs over the past several decades. Systematically reviewing these key technological advances helps to understand the developmental trajectory of GFCs and provides a solid foundation for future research and applications. Figure 2 presents the important milestones in the development of GFCs, reflecting the evolution

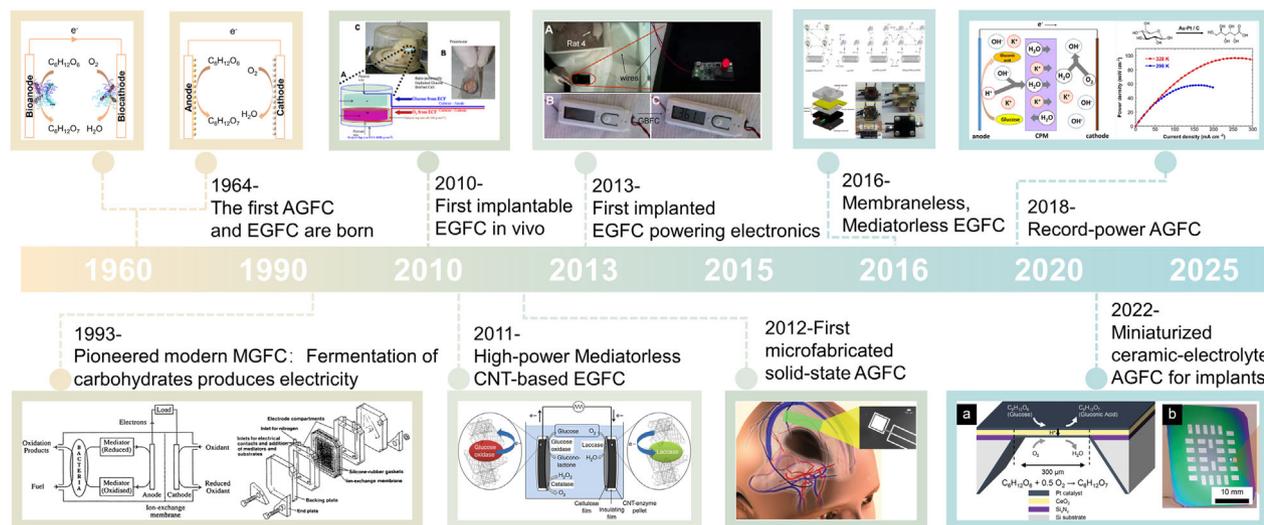


Figure 2. Key development processes in GFCs. The first AGFC^[15] and EGFC^[16] are born. Pioneering modern MGFC: Fermentation of carbohydrates produces electricity, Reproduced with permission.^[17] Copyright 1993, Springer Nature. First implantable EGFC in vivo. Reproduced with permission.^[18] Copyright 2010, Open Access. High-power Mediatorless CNT-based EGFC. Reproduced with permission.^[19] Copyright 2011, Springer Nature. First microfabricated solid-state AGFC. Reproduced with permission.^[20] Copyright 2012, Open Access. First implanted EGFC powering electronics. Reproduced with permission.^[21] Copyright 2013, Springer Nature. Membraneless, mediatorless EGFC. Reproduced with permission.^[22] Copyright 2016, Springer Nature. Record-power AGFC. Reproduced with permission.^[23] Copyright 2018, Open Access. Miniaturized ceramic-electrolyte AGFC for implants. Reproduced with permission.^[24] Copyright 2022, John Wiley and Sons.

from the initial enzymatic and abiotic systems to modern miniaturized and integrated devices.

In 1964, Yahiro et al. invented the first EGFC by using glucose oxidase and laccase on electrodes. Bockris et al. simultaneously created the first AGFC by directly oxidizing glucose with Pt. In 1993, Allen and Bennetto pioneered modern microbial glucose fuel cells, generating electricity from carbohydrate fermentation via mediators, which re-ignited interest in biofuel cells. In 2010, Cinquin et al. first implanted an EGFC in a rat, which could produce about 6.5 μW of power continuously for months at 0.13 V, proving the feasibility of generating electricity from physiological glucose. In 2011, Zebda et al. developed a high-power EGFC based on CNT, providing an open-circuit voltage of 0.95 V and a peak power of 1.3 mW cm^{-2} . In 2012, Rapoport et al. invented the first microfabricated solid-state AGFC, supporting microfabrication design and IC integration. In 2013, Zebda et al. implanted an EGFC in a rat's abdomen to power an LED and a thermometer. In 2016, Christwardana et al. developed a membrane- and mediator-free EGFC, achieving a peak power density of 102.0 $\mu\text{W cm}^{-2}$ by optimizing electrolyte flow rates. In 2018, Torigoe et al. achieved a record peak power density of 95.7 mW cm^{-2} by changing the catalyst composition in an alkaline medium. In 2022, Rupp's team invented a miniaturized ceramic-electrolyte glucose fuel cell for implantation, offering long-term stability and high integration for implantable electronics. These events show the progression of GFCs from invention toward potential practical applications.

2.2. Working Principle of GFCs

In GFCs, electrical energy is generated through electrochemical reactions between the fuel and oxidizer at two spatially separated electrodes. Electrons released during the electro-oxidation

of the fuel flow from the anode through an external load circuit to the cathode, where terminal electron acceptors are reduced. This electron flow is driven by the electrochemical potential difference between the anode and cathode redox pairs.^[25]

At the anode, glucose is catalytically dehydrogenated to form gluconolactone, releasing electrons and protons. The lactone is subsequently hydrolyzed to gluconic acid,^[26] and the electrons are transferred to the electrode via direct catalyst transfer or mediator-assisted transfer. The choice of catalysts and regulation of the reaction environment are critical for enhancing oxidation efficiency. In the cathodic oxygen reduction reaction, O_2 is reduced to H_2O under acidic/neutral conditions and OH^- under alkaline conditions. Platinum-like catalysts accelerate the dissociation of reactants through surface active sites,^[27] while enzyme catalysts utilize biologically active centers to directly transfer electrons and lower energy barriers.^[28] Both types of catalysts optimize the electron transfer path.

During the reaction, protons travel from the anode to the cathode through the electrolyte, while electrons move from the anode to the cathode via an external circuit to power the external device. Both protons and electrons take part in the reduction process at the cathode, thus facilitating the transformation of chemical energy into electrical energy. The electron flow is facilitated by the conductive pathway, and protons migrate through the ion channels. The activity of the catalyst and the structure of the electrolyte work together to ensure efficient transfer.

The performance of the GFC is determined by several factors, including catalyst activity, electron transfer pathways (direct or mediator-assisted), electrolyte properties (such as proton conduction and internal resistance), and the balance between reactant supply and demand (optimization of glucose and O_2 concentrations). Catalyst design must account for the electronic structure and stability of the active site, while the electrolyte should be

Table 1. Performance comparison of different types of GFCs.

Tapes	Anode	Cathode	OCV [V]	J_{\max} [$A\ m^{-2}$]	P_{\max} [$mW\ m^{-2}$]	Lifetime	Refs.
MGFC	Paper@Ni- <i>Bacillus stratosphericus</i>	Paper@C	0.3	7	150	Not available	[29]
MGFC	Ni-Escherichia coli	Not available	Not available	Not available	52	Not available	[30]
EGFC	GOx/AuNPs/PTFE/CP	Lac/SWCNTs/PTFE/CP	0.6	Not available	96.4	Retain 75% power after 2000s	[31]
EGFC	(GOx-(PVI-Os-dmo)-SWCNTs) ₃ -(GOx-(PVI-Os-dmo)) ₃ /Aga-TREH)	BOD-(PAA-PVI-Os-dCl)-SWCNTs	0.66	Not available	150	Not available	[32]
AGFC	Al/Au/ZnO	Pt	0.84	1.11	162	100% retention for 9 h running	[33]
AGFC	Pt and Pd graphene	N-doped GO nanoribbons	0.216	Not available	249	About 92% retention after 7 days	[34]
AGFC	PtNi alloy	Pd	0.35	Not available	≈28.3	Not available	[35]
HGFC	GOx	Prussian Blue	Not available	9	440	retain 97% of its operating voltage after 20 charge/discharge cycles	[36]
HGFC	Pt-C	CNT/PEI/IPA-Hemin/GOx	0.65	0.861	660	Retain 67% of its initial catalytic activity after 2 weeks.	[37]
HGFC	H-CoNC/CNT/GOx	Pt	0.473	3.16	2030	Retain 80% of its initial catalytic activity after 2 weeks.	[38]

adapted to the reaction environment to minimize resistance to ion migration. Additionally, reactant concentration must be managed to prevent electrode polarization, ensuring efficient and stable energy conversion.

2.3. Types of GFCs

In general, GFCs can be categorized into four main types based on the type of catalyst used for the electrode reaction and the electrode structure: MGFCs, EGFCs, AGFCs, and HGFCs. EGFCs utilize isolated enzymes such as glucose oxidase and laccase, whereas MGFCs employ the entire enzyme system of electroactive microorganisms. AGFCs primarily rely on abiotic catalysts, including noble metals or transition metals. By contrast, HGFC integrates both enzymatic and abiotic catalysis to create a synergistic system that enhances stability, power density, and biocompatibility. The performance comparison of various types of GFCs is summarized in **Table 1**.

2.3.1. MGFCs

The core principle of MGFCs is to drive the glucose oxidation process in biomass or various organic wastes through the catalytic effect of microorganisms, efficiently converting the biochemical energy contained therein into electrical energy.^[39] The infrastructure of an MGFC consists of an anode and a cathode. Typically, an exchange membrane is placed between the two electrodes to inhibit the diffusion of medium, reduce unnecessary flux between the electrodes, prevent contamination of the electrode surfaces by microorganisms during long-term operation, and maintain the ionic conductivity. Within the anode chamber, electrochemically active microorganisms are firmly attached to support electrodes, which can be made from a wide range of carbon-based materials,

such as carbon fiber,^[40] carbon cloth,^[41] carbon graphite,^[42] and carbon nanotubes.^[43] Biofuels utilized in MGFCs include various forms of wastewater,^[40,44] marine sediment soil,^[45] freshwater soil, and activated sludge.^[46]

Choi et al.^[47] developed a paper-based MGFC sensor that utilizes the glucose-dependent germination of *Bacillus subtilis* spores in potassium-rich body fluids such as sweat (**Figure 3A**). The dormant state of the spores ensures a long shelf life, and they metabolically produce electricity upon germination in the presence of glucose, enabling self-powered signal conversion. The device integrates microfluidic and LED alarm circuitry, emphasizing its low-cost and flexible advantages. Moreover, the system benefits from a biological self-repair mechanism, supporting stable and long-lasting monitoring.

In addition, Li et al.^[48] displayed a microfluidic MGFC based on AC@N-GA/rGO@Ni electrodes, which achieves a near 4e⁻ oxygen reduction reaction pathway via nitrogen-doped aerogel composite activated carbon. This is combined with a 3D nickel foam anode to enhance bacterial loading, resulting in a volumetric power density of 1181.0 W m⁻³ in a membrane-less architecture (**Figure 3B**). The system provides high-performance, low-cost power for miniature bioelectronic devices.

Beyond material and architectural innovations, recent advancements have also focused on genetically engineering microbial strains to enhance metabolic efficiency and power output in MGFCs. Song's team genetically reprogrammed *Shewanella oneidensis* to reconfigure the glucose transport, the Entner-Doudoroff pathway, and the lactate co-metabolism pathway.^[44] This modification resulted in a glucose utilization rate of 230.9 mg L⁻¹ h⁻¹ for the engineered strain G₇ΔRSL₁. When combined with a biofilm thickening strategy and a rGO/CNT 3D hybrid electrode, the system exhibited reduced charge transfer resistance to 110 Ω. Peak power densities of 560.4 and 373.7 mW m⁻² were achieved in artificial and actual leas wastewater (**Figure 3C**), respectively, setting a record for the performance

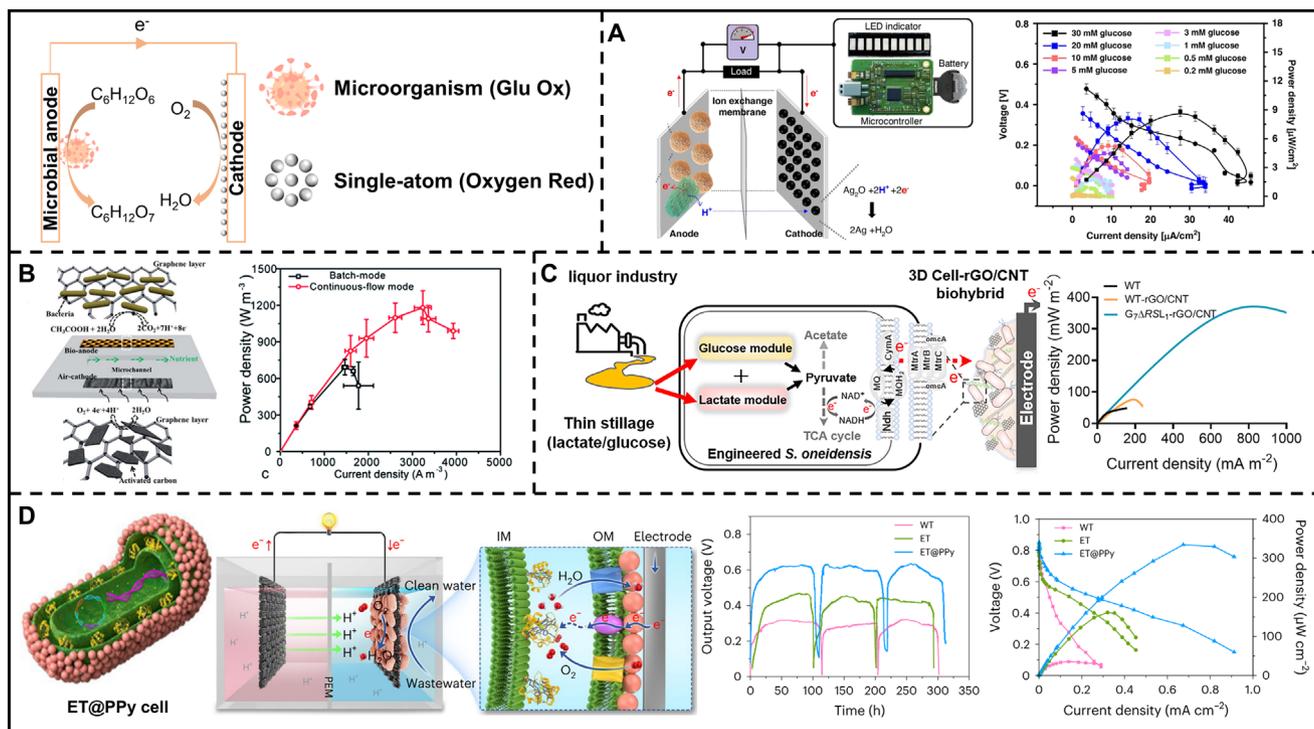


Figure 3. Examples of typical MGFCs. A) The selective and sensitive germination of *Bacillus subtilis* spores in potassium-rich body fluids is harnessed to convert the germination rate and metabolic activity of budding cells into measurable electrical output in a MGFC. Reproduced with permission.^[47] Copyright 2024, Springer Nature. B) A 3D nitrogen-doped graphene aerogel-activated carbon composite catalyst enables low-cost microfluidic MGFCs with exceptional performance. Reproduced with permission.^[48] Copyright 2016, The Royal Society of Chemistry. C) Engineered *Shewanella oneidensis* G₇ΔRSL₁-rGO/CNT biohybrid for enhanced power recovery from thin stillage via co-utilization of glucose and lactate. Reproduced with permission.^[44] Copyright 2022, Elsevier. D) A high-performance MGFC utilizes sustainable *Escherichia coli*-based cathodic biocatalysts for rapid wastewater treatment and competitive power output. Reproduced with permission.^[49] Copyright 2024, Springer Nature.

of engineered *S. cerevisiae* microbial fuel cells. Meanwhile, Bai et al.^[49] developed a genetically engineered *E. coli*-based cathodic catalyst and exhibited excellent oxygen reduction reaction activity, thereby accelerating the decontamination of organic matter in sewage sludge. Notably, glucose consumption reached up to 19.4 mM over 100 h, with a maximum power density of 334.0 $\mu\text{W cm}^{-2}$ (Figure 3D).

The electron transfer in MGFCs primarily occurs via two pathways: direct contact between bacterial pili and the electrodes, enabling short-distance electron transfer,^[50] and indirect electron transfer facilitated by electronic conductors.^[51] These mechanisms enable the bioelectrochemical conversion of glucose into electricity.

MGFCs offer significant advantages in waste treatment and environmental protection. Electroactive microorganisms exhibit strong resistance to toxicity and maintain stability under normal operating conditions, making MGFCs durable and less prone to loss of activity.^[52] Additionally, the continuous reproduction of microbial populations helps to slow down the depletion of catalytically active elements, thereby extending the service life of the device.

Despite their promising role in waste treatment and environmental energy harvesting, MGFCs face significant barriers to biomedical translation. A key technical limitation lies in their low power output and the difficulty in precisely controlling the electron transfer pathways within microorganisms, both of which

hinder energy conversion efficiency and device scalability. More critically, from a biomedical perspective, MGFCs face fundamental biosafety and compatibility issues. Many electroactive microorganisms are potentially pathogenic, and their colonization in the human body may trigger immune responses or infections. Moreover, the need to maintain microbial viability and function under sterile, physiologically relevant conditions poses additional challenges. Consequently, current MGFC systems exhibit limited biocompatibility and still face significant biosafety challenges for biomedical applications.

Nevertheless, advances in synthetic biology and genetic engineering may provide new opportunities to overcome these limitations. Through targeted genetic modifications, it is possible to reprogram microorganisms into non-pathogenic, highly efficient electroactive strains with reduced immunogenicity. Such engineered microbes could pave the way for future MGFCs that are safe and functional within the human body, enabling their eventual use in implantable biosensors or bioelectronic therapies.

2.3.2. EGFCs

EGFCs are typically composed of two enzyme-functionalized bioelectrodes, with the core principle involving the catalysis of oxidation or reduction reactions by enzymes. During these reactions, the catalytic centers of the enzymes undergo corresponding

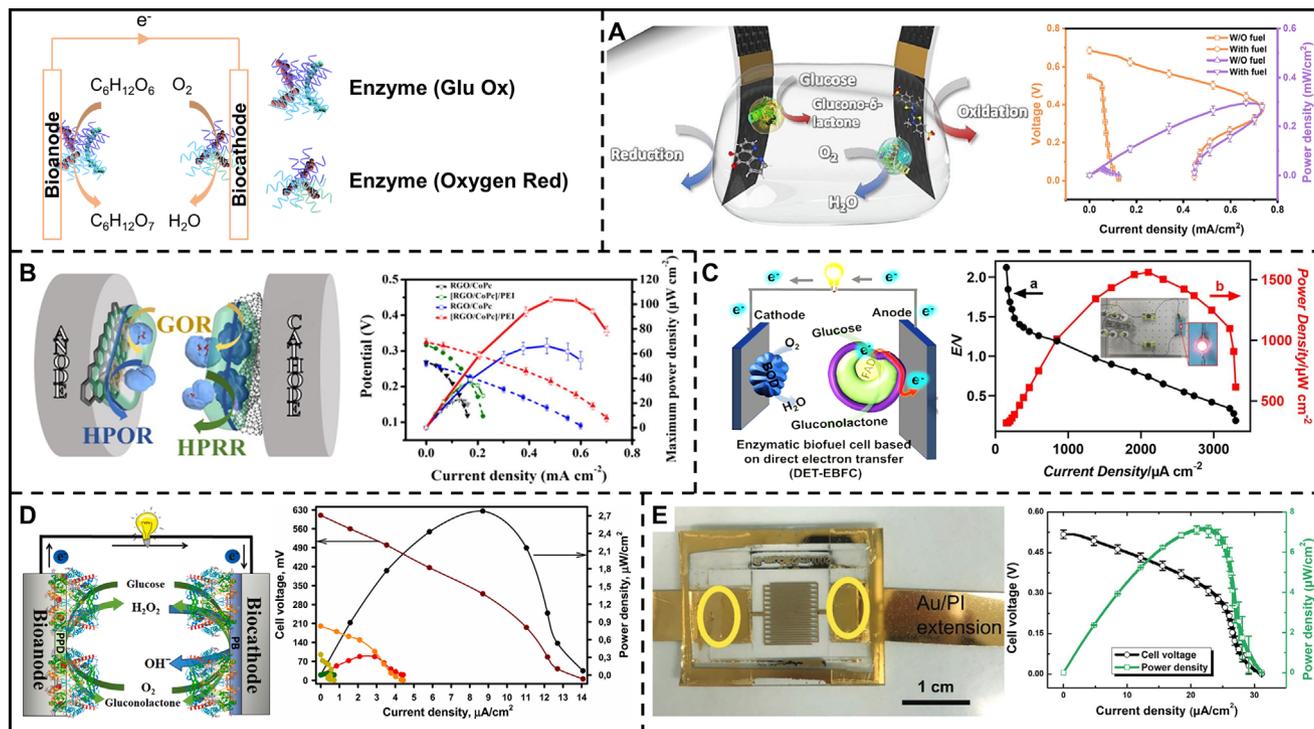


Figure 4. Examples of typical EGFCs. A) EGFCs combined with supercapacitors as hybrid energy devices exhibit unique self-charging properties, demonstrating high fuel reaction rates and excellent power and storage capacities. Reproduced with permission.^[54] Copyright 2024, Elsevier. B) An anode catalyst based on amine-coordinated cobalt phthalocyanine enhances EGFCs, and amine axial ligands effectively improve EBC performance. Reproduced with permission.^[55] Copyright 2020, Elsevier. C) An EGFC based on conductive enzyme nanocapsules *n*(GOx-PPy) demonstrates enhanced power output and stability. Reproduced with permission.^[56] Copyright 2021, Elsevier. D) A membrane-free EGFC using graphite rod electrodes, Prussian blue nanoparticles, and glucose oxidase achieves an OCV of 646 mV and a power density of 10.9 $\mu\text{W cm}^{-2}$. Reproduced with permission.^[57] Copyright 2022, Elsevier. E) A stretchable EGFC based on a microfluidic structure with a flexible PDMS substrate and wrinkled Au electrodes enhances stretchability and catalyst loading. Reproduced with permission.^[58] Copyright 2023, John Wiley and Sons.

redox changes. The unique properties of these enzymes distinguish EGFCs from MGFCs. The high substrate specificity of the enzymes and their ability to be immobilized on the electrode eliminate the need for a membrane to separate the anodic and cathodic fluids.^[53] This not only simplifies the cell's configuration but also lays the foundation for its miniaturization. However, natural enzymes suffer from several inherent limitations, including susceptibility to denaturation, poor long-term operational stability, and inefficient electron transfer to the electrode surface. These issues pose major obstacles to the development of high-performance, durable EGFCs, particularly for biomedical applications.

Recent studies have focused on addressing these bottlenecks through strategies such as optimizing electrode structure, enhancing catalytic materials, and integrating bio-hybrid systems. The following examples highlight representative advancements in these areas (Figure 4).

Innovations in enzyme electrode structures continue to drive the development of EGFCs. Kwon et al.^[54] have innovatively developed enzyme-dielectric synergistic flexible hybrid energy devices that integrate the functions of a biofuel cell and a supercapacitor, and the hybrid energy devices are self-charging and capable of sustained discharging when no fuel is available, which opens up a new path to energy supply for wearable and implantable medical devices (Figure 4A).

In order to improve the power density of EGFCs, Chung et al.^[55] developed a CoPc catalyst with axial coordination of PEI amine ligands. With Co-N donor–acceptor coupling, a power density of 25.4 $\mu\text{W cm}^{-2}$ was achieved in EGFCs, and 85.2% operational stability was maintained within 24 h (Figure 4B). And, Zhu's team formed conductive-protective integrated nanocapsules by in-situ polymerization of pyrrole triggered by glucose, so that the power density of the constructed enzyme fuel cell reached 647.2 $\mu\text{W cm}^{-2}$, which was 245 times higher than that of natural enzyme, and the performance remained 94% after 15 days (Figure 4C).^[56] In addition, the single enzyme EGFC constructed by Ramanaviciene et al.^[57] based on GOx-catalyzed glucose oxidation and PB-catalyzed H_2O_2 reduction, measured an open circuit voltage of 646 mV, a maximum power density of 10.9 $\mu\text{W cm}^{-2}$, and a current density of 60.5 $\mu\text{A cm}^{-2}$ in 40 mM glucose (Figure 4D).

In the field of flexible and stretchable EGFCs, Khang et al.^[58] used a microfluidic PDMS substrate to pre-stretch the gold electrode to form wavy wrinkles, expand the specific surface area, increase the catalyst loading, and then increase the cathode and anode reaction rate. Combined with the fork channel capillary self-filling technology to achieve catalyst isolation and uniform distribution, the maximum power density reached 7.1 $\mu\text{W cm}^{-2}$ without stretching, and the power density can also reach 5.4 $\mu\text{W cm}^{-2}$ under external stretching, providing stable and flexible

energy support for wearable devices (Figure 4E). These studies have innovated the structure of enzyme electrodes from different dimensions, providing a new design scheme for the development of high power, long life, and flexibility of EGFCs.

In EGFCs, enzymes such as glucose oxidase (GOx)^[32,59] or glucose dehydrogenase (GDH)^[60] are commonly used at the anode, while laccase (Lac)^[19] or bilirubin oxidase (BOD)^[52] are often employed at the cathode. The key advantages of EGFCs include their lack of requirement for electrode compartmentalization, simpler design, and potential for miniaturization, making them suitable for applications in biosensors and implantable devices, while also achieving high power density. However, enzymes, due to their complex protein structures, are prone to inactivation over time, which limits their long-term applicability.^[61]

And in EGFCs, bioelectrodes utilize the electron transfer (ET) pathways of oxidoreductases. Enzymes are macro molecules with a catalytic center that is mostly encapsulated by an electrically inert protein shell. A redox enzyme catalyzes the fuel oxidation or oxidant reduction, and the catalytic center is reduced or oxidized, respectively.^[62] To reset the redox state of a catalytic center for the next biocatalytic cycle, an electron acceptor or donor is usually used.^[43] In bioelectrochemistry, inorganic electrodes are used to manipulate external electrons, thereby serving as the artificial electron acceptor/donor for the enzyme.^[53] Enzymatic bioelectrochemical processes can operate through either direct electron transfer (DET) or mediated electron transfer (MET) mechanisms.^[63] DET refers to the process of electron transfer between the catalytic center of an enzyme and the surface of an inorganic electrode via electron tunneling, without the need for an electron mediator. In contrast, MET requires the use of a small molecule or metal complex as an electron carrier. According to quantum mechanical ET theory, the ET rate decreases exponentially with the electron tunneling distance,^[64] and an upper threshold of 1.4 nm is required for feasible ET.^[65] DET occurs only when the catalytic center of the enzyme is close enough to the electrode within the threshold electron tunneling distance.^[66] Taking BOD as an example, it embraces four copper atoms, which can be categorized into three types, with trinuclear T2/3 Cu as the oxygen reduction site. T1 Cu, communicating with the trinuclear cluster by means of intramolecular ET, is located a short distance from the protein surface, permitting rapid DET.^[67] In contrast, another common enzyme, GOx, contains a flavin active center located at least 1.7 nm away from the protein surface,^[68] hindering DET and requiring MET through an artificial mediator.

EGFCs hold great promise for energy conversion and biomedical applications due to their unique advantages. Nevertheless, further research into enzyme activity, stability, and electron transfer efficiency is essential to address current challenges and explore innovative solutions for large-scale applications and commercialization.

2.3.3. AGFCs

AGFCs employ abiotic catalysts, typically precious metals or their alloys, to facilitate internal reactions. These fuel cells offer significant advantages over the first two types: they can be sterilized using standard methods, exhibit excellent thermal stability,^[69]

and ensure biocompatibility by selecting specific catalysts, making them suitable for biomedical applications. However, AGFCs commonly rely on noble metal catalysts to oxidize glucose, which presents several limitations. These include the high cost of the catalysts, electrode susceptibility to poisoning.^[70] And, in most cases, these catalysts primarily cleave the C-H bond to form gluconic acid, thereby utilizing only two available electrons. This two-electron transfer process is observed in various electrocatalysts, such as platinum,^[71] gold,^[72] and bimetallic electrodes.^[73] To address these challenges, researchers have developed a range of AGFC configurations with improved architecture, materials, and integration strategies (Figure 5).

Simons et al.^[24] investigated a AGFC based on the proton-conducting electrolyte ceria (Figure 5A), which features separate membranes no thicker than 400 nm. This cell is fully integrated into silicon, enabling easy integration with bioelectronics applications. The results indicate that this miniature, ceramic-based glucose fuel cell is the smallest potential implantable power source to date, offering a viable option for powering the next generation of highly miniaturized implantable medical devices.

Moreover, Fussenegger's team designed an implantable AGFC that uses a novel copper-containing, conductively tuned, 3D carbon nanotube composite.^[74] This cell constantly tracks blood glucose concentrations, transforms surplus glucose into electrical energy when hyperglycemia occurs, and produces enough energy to trigger opto-electronically genetically engineered β -cells, prompting them to release vesicular insulin (Figure 5B).

Nowadays, some researchers are working to enhance the performance of AGFCs through innovative electrode structure design. For example, Su et al.'s research team developed a capacitive MXene-based self-feeding sensor for biofuel cells (Figure 5C).^[75] The sensor employs a $\text{Ti}_3\text{C}_2\text{T}_x/\text{AuNPs}/\text{PPy}$ ternary heterojunction as the anode. Experiments have demonstrated that the sensor exhibits excellent stability and strong anti-interference ability, with recoveries in environmental and biological samples ranging from 93.8% to 108.8%. These results strongly contribute to the further development of AGFC technology in practical applications.

In addition, Li et al.^[76] pioneered the "self-supporting enzyme mimetic electrode + nested coaxial structure" biofuel cell, the cathode obtains laccase-like activity through ion etching-electrical grafting, and the anode realizes GOx mimicry through low-temperature solvent thermal loading of AuNPs. The four-layer tandem structure outputs 1.7 V open-circuit voltage and 3639.0 $\mu\text{W cm}^{-2}$ ultra-high power density, with 15-day stability of over 90%, breaking through the enzyme electrode interface limitations and power bottleneck (Figure 5D).

Currently, many researchers opt for platinum-based Raney electrodes^[77] as anodes due to their superior chemical stability, roughness coefficients that are at least an order of magnitude higher than those of commercial platinum foils, their ability to more accurately reflect the glucose oxidation potential, and their reduced sensitivity to dissolved oxygen.

Although nickel was previously used as a removable element in platinum-based Raney electrodes,^[78] research has increasingly shifted toward more biocompatible elements, such as Zn,^[77] due to concerns over nickel's biocompatibility. Zinc-based electrodes exhibit improved performance in oxygen-free environments; however, they still experience degradation over time and

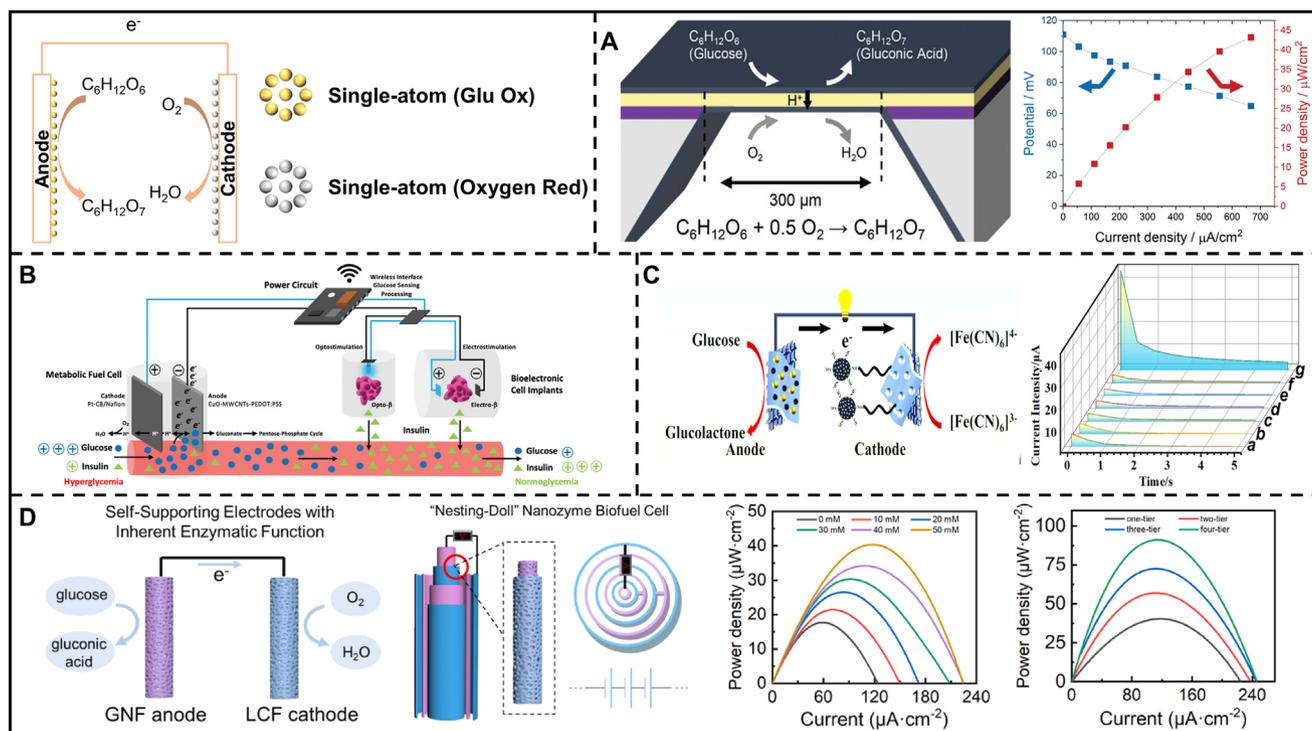


Figure 5. Examples of typical AGFCs. A) Proton-conducting ceramic GFCs, integrated with silicon and offering unprecedented miniaturization, exhibit high-temperature stability and excellent electrochemical performance. Reproduced with permission.^[24] Copyright 2022, John Wiley and Sons. B) An implantable GFC, utilizing a copper-doped, conductivity-tuned 3D carbon nanotube composite, effectively monitors and regulates blood glucose levels by converting excess glucose into electrical energy. Reproduced with permission.^[74] Copyright 2023, John Wiley and Sons. C) An EGFC self-powered sensor, utilizing a ternary heterostructure based on Ti_3C_2Tx MXene with gold nanoparticles and polypyrrole nanoparticles, offers high sensitivity for detecting DEHP in complex environments and biological samples. Reproduced with permission.^[75] Copyright 2025, Elsevier. D) A new integrated strategy for designing independent electrodes with inherent enzyme-like activity and high electrical conductivity eliminates the limitations of the enzyme-electrode interface. Reproduced with permission.^[76] Copyright 2024, Elsevier.

show poor tolerance to interstitial fluids. Rapoport et al.^[20] employed a Pt/Al Raney electrode, but this configuration is more suitable for use as a cathode. Recently, highly porous platinum-based electrodes with enhanced roughness coefficients have been developed through cyclic or pulsed electrodeposition of Pt-Cu alloys.^[73] These electrodes can be fabricated at room temperature.

Nonetheless, the susceptibility of platinum electrodes to poisoning during glucose oxidation remains a significant issue. Endogenous substances in body fluids, particularly amino acids, strongly affect platinum electrodes. Therefore, creating novel alloy catalysts to boost catalytic performance and minimize poisoning risks, or utilizing protective coatings to block amino acid diffusion, has become a critical research direction for AGFCs.

2.3.4. HGFCs

HGFCs are composite fuel cell systems that integrate enzyme catalysis with abiotic catalysis. The primary goal is to efficiently convert the chemical energy in glucose into electrical energy through a synergistic catalytic mechanism. By leveraging the complementary strengths of both catalytic modes, HGFCs aim to address the limitations of traditional single-catalytic systems, including poor stability, low power density, and insufficient bio-

compatibility. Representative HGFCs developed for research and practical applications are illustrated in **Figure 6**.

The first class of HGFCs that rely on the enzyme anode to catalyze glucose oxidation. For example, Cho et al.^[79] studied a novel dielectric-free multilayer HGFC. The HGFC utilizes assembly induced by the interfacial interactions between hydrophilic GOx and hydrophobic conductive indium tin oxide nanoparticles (ITONPs) with unique shapes, along with a multilayer electrode system. The cathode was prepared by sputtering Pt onto the main electrode. The multilayer fiber optic electrode system exhibits high power output ($\approx 10.4 \text{ mW cm}^{-2}$) and excellent operational stability (Figure 6A). Later, Cho's team has once again achieved high power HGFCs through a new strategy that utilizes electron transfer to enhance the redox mediator (RM) layer.^[80] This process is ubiquitously facilitated by covalently bridged metal nanoparticles between neighboring RMs. The electron transfer properties are enhanced not only within the RM layer itself but also at the GOx/host electrode and GOx/GOx interfaces. This results in a significant improvement in the performance of the enzyme anode (Figure 6B). HGFCs constructed with innovative anodes and Pt-based cathodes demonstrate high power output and excellent operational stability.

The second class of HGFCs that rely on monatomic anodes to catalyze glucose oxidation. Dong et al.^[81] successfully designed an abiotic anode based on rhodium single-atom nano-enzymes

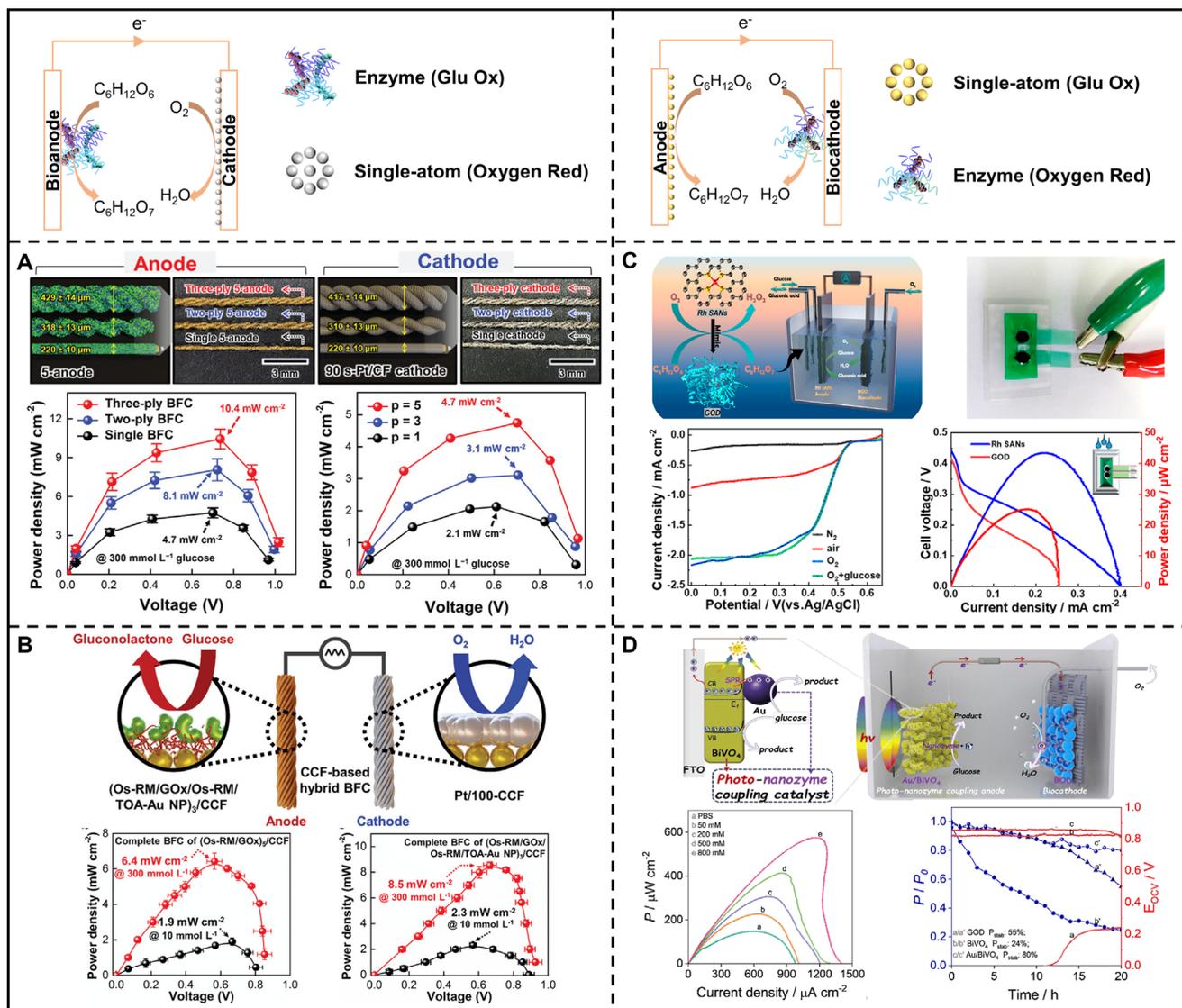


Figure 6. Examples of typical HGFCs. A) A novel mediator-free multilayer GFC based on enzyme electrodes overcomes low electron transfer efficiency and poor stability by assembling hydrophilic glucose oxidase and hydrophobic indium tin oxide nanoparticles onto a carbon nanotube and AuNP anode, coupled with a Pt-sputtered cathode. Reproduced with permission.^[79] Copyright 2023, John Wiley and Sons. B) A novel strategy using covalent bridging of metal nanoparticles to enhance redox mediator layers significantly improves electron transfer, boosts enzyme anode performance, and when combined with a Pt-based cathode, forms a HGFC with high power output and exceptional stability. Reproduced with permission.^[80] Copyright 2024, John Wiley and Sons. C) A rhodium single-atom anode, mimicking natural glucose oxidase, coupled with a bilirubin oxidase biocathode, enhances both the biometabolism and electrometabolism of Glu Ox. Reproduced with permission.^[81] Copyright 2023, American Chemical Society. D) An Au/BiVO₄ photoelectron-catalytic nanozyme with triple synergistic effects enhances light absorption, electron transfer, and stability. Reproduced with permission.^[82] Copyright 2024, The Royal Society of Chemistry.

(RhSANS) and coupled it with a BOD biocathode to construct a novel HGFC tested, the cell demonstrated excellent performance with a maximum power density of up to $135.0 \pm 3.0 \mu\text{W cm}^{-2}$, which achieved nearly twofold significant increase in power density compared to the cell demonstrated excellent performance with a maximum power density of $135.0 \pm 3.0 \mu\text{W cm}^{-2}$, which is nearly twice as high as that of the conventional natural GOx-based EGFC (Figure 6C). Moreover, Zhu's team developed an Au/BiVO₄ photovoltaic synergistic nano-enzymatic catalyst, which enhances the BiVO₄ carrier density through the incorporation of Au. Meanwhile, the 3D structure of BiVO₄ in-

creases the Au loading and improves catalytic stability. The catalyst was applied to the GFC anode and worked synergistically with the BOD biocathode to efficiently convert solar energy into glucose chemical energy. The system achieved a power density of $575.0 \mu\text{W cm}^{-2}$ and an open-circuit voltage of 0.86 V, with stable operation for 20 h (Figure 6D).^[82] This innovative photovoltaic-coupled nano-enzymatic catalytic strategy significantly expands the performance limits of GFCs.

HGFC provides an innovative path for efficient energy conversion by integrating the synergistic advantages of enzyme catalysis and abiotic catalysis. Its ability to optimize catalytic efficiency and

enhance stability not only breaks through the bottleneck of traditional monocatalytic systems, but also opens up a new direction for energy supply of wearable and portable devices. In the future, with the continuous innovation of catalytic materials and the improvement of system integration technology, HGFC is expected to realize large-scale application in personalized medicine and other fields, and become a key force to promote the development of new energy technology.

3. Physiological Sources of Glucose

Physiological glucose sources refer to biofluids that naturally exist and circulate within the human body, including blood, interstitial fluid, sweat, saliva, and tears, which provide a continuous and stable supply of glucose for GFCs. These fluids provide a sustainable and biocompatible glucose supply, making them ideal candidates for powering GFCs, particularly in applications related to implantable medical devices, continuous health monitoring systems, and wearable electronics.

However, variations in glucose concentration, accessibility, secretion mechanisms, and biochemical composition among different biofluids pose distinct challenges and opportunities for GFC integration. For instance, blood and interstitial fluid offer relatively high and stable glucose levels suitable for implantable applications, while sweat and saliva are more amenable to non-invasive, skin-interfaced systems despite their lower and more variable glucose content. Understanding the properties and constraints of each biofluid is essential for optimizing GFC design, enhancing energy conversion efficiency, and expanding the practical use of GFCs in healthcare, personalized medicine, and next-generation self-powered biosensors. By analyzing and comparing the advantages and limitations of each biofluid in detail, this section aims to offer a comprehensive theoretical foundation and practical guidance for the rational design and deployment of next-generation GFCs.

3.1. Blood

Blood is the most obvious choice as a physiological source of glucose to drive GFCs, owing to its relatively high and stable glucose concentration, typically ranging from 3.9 to 5.6 mM under normoglycemic conditions.^[14] More importantly, the continuous replenishment and renewal process through the circulatory system provides a steady supply of glucose to the fuel cell, ensuring that it can meet power output requirements over time. This inherent stability and availability make blood an attractive energy source, particularly for implantable or in vivo GFC applications.

In the medical field, blood sampling technology and related equipment are well-developed, making it easy to obtain blood samples for fuel cell operation. Additionally, existing medical monitoring equipment can monitor and regulate blood glucose levels and other key indicators in real time, facilitating better management and optimization of the fuel cell's operation.^[83,84] Such synergy between existing medical technologies and GFCs enhances the feasibility of using blood as a reliable power source in practical biomedical scenarios.

A notable example is the work of Takeo Miyake's team, who invented a needle-type EGFC using enzyme/mediator/CNT composite fibers (Figure 7C). The power generated by blood glu-

cose in the mouse heart was 16.3 μW at 0.29 V, demonstrating the feasibility of in vivo energy harvesting directly from blood glucose.^[85]

Despite these advantages, blood-based GFCs face significant challenges. Blood collection requires invasive procedures,^[91] such as piercing the skin and blood vessels, which can cause pain and discomfort for the user and may increase the risk of infection. These factors limit the feasibility of frequent sampling and long-term use. Furthermore, the complex biochemical composition of blood poses electrochemical challenges. Blood contains various proteins, lipids, and cellular components that may adsorb onto electrode surfaces, forming biofouling layers that hinder effective contact between glucose and the catalyst. These substances can also interfere with the glucose oxidation process, reducing the fuel cell's efficiency and stability, ultimately degrading electrode performance and affecting the overall fuel cell performance.

To address these issues, current research is focusing on the development of antifouling electrode materials, selective membranes, and surface modification strategies that resist protein adsorption while maintaining efficient glucose transport and catalytic activity. These innovations are key to unlocking the full potential of blood-powered GFCs for next-generation implantable and autonomous biomedical devices.

3.2. Tissue Fluid

In addition to traditional blood-based assays, tissue fluid has emerged as a compelling alternative glucose source for GFCs. As the immediate extracellular environment surrounding cells, tissue fluid more accurately reflects the glucose levels required for cellular metabolism, making tissue fluid a physiologically responsive and reliable energy source. Tissue fluid-based GFCs can be more directly coupled with the body's physiological metabolic processes, providing energy support that is closer to the physiological needs of implantable medical devices and similar applications. Recent studies have shown strong correlations between the levels and temporal characteristics of glucose present in tissue fluid and blood plasma. While normal blood glucose levels range from 3.9 to 5.6 mM, the glucose concentration in tissue fluid is approximately 3.3–3.6 mM,^[13] making it one of the highest biofluids outside of blood, suitable for driving GFCs effectively. For instance, Wang et al.^[90] designed a gel microneedle bioelectrode based on enzymatic polymerization of a carbon fiber interface for real-time, continuous monitoring and prediction of biomarkers in interstitial fluids of living animals (Figure 7F). Moreover, the mathematical model proposed by Steil, Rebrin, and their colleagues sheds light on the kinetics and correlation between glucose levels in blood and tissue fluid, further supporting its role in real-time monitoring applications.^[92,93]

Notably, interstitial fluid (ISF) offers a promising alternative to blood as a physiological glucose source for GFCs, owing to its stable glucose content, lower sampling invasiveness, and better physiological compatibility. These advantages make ISF particularly suitable for integration into minimally invasive sensors and implantable systems, enabling continuous and biocompatible energy harvesting for smart medical devices.

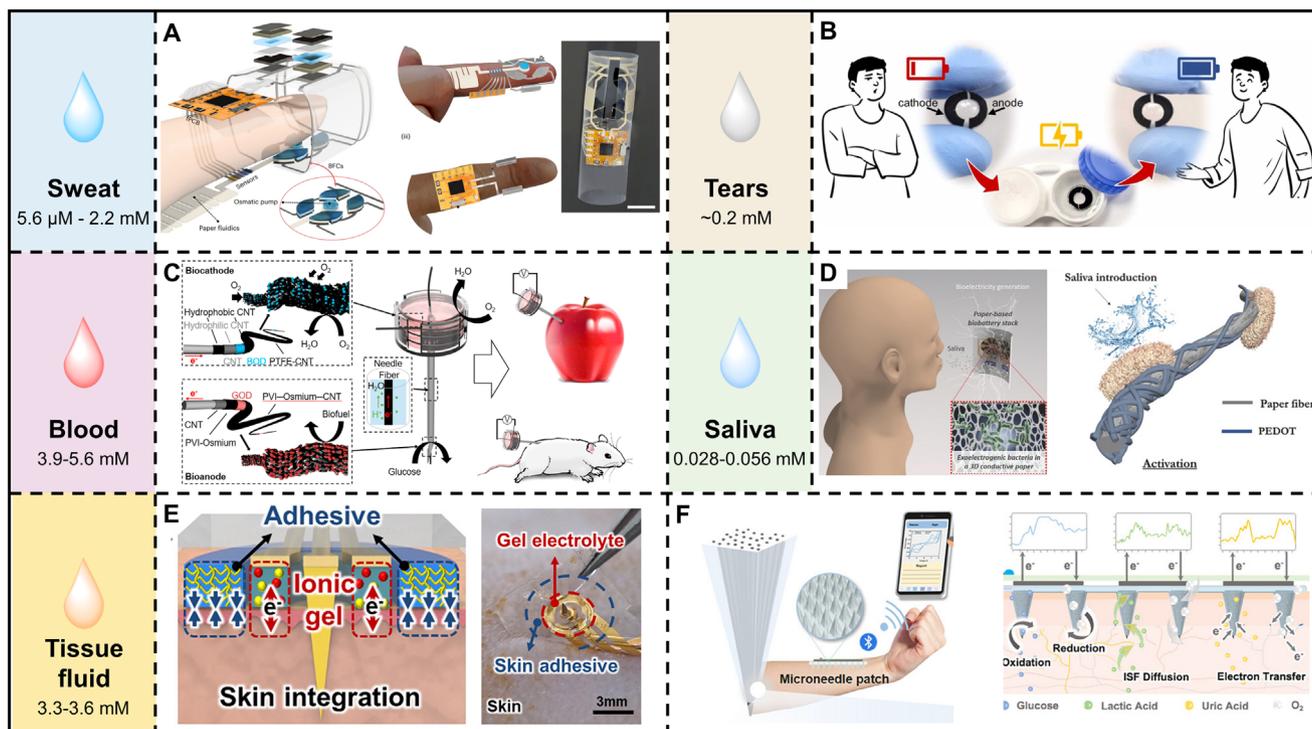


Figure 7. Physiological sources of glucose that can be utilized to power GFCs. A) A self-sustained, continuous sweat-sensing system driven by fingertip sweat, utilizing EGFC and AgCl-Zn battery to harvest and store bioenergy. Reproduced with permission.^[86] Copyright 2024, Springer Nature. B) A secure tear-based battery integrated into contact lenses, charged by biofuels during storage within the lens. Reproduced with permission.^[87] Copyright 2023, Elsevier. C) A needle-shaped GFC using enzyme/mediator/CNT composite fibers exhibits high current density in 5 mM artificial blood glucose, generating 16.3 μW of power from blood glucose in the mouse heart at 0.29 V. Reproduced with permission.^[85] Copyright 2020, Elsevier. D) A micro-power source that can be integrated into paper-based diagnostic devices and activated with a single drop of saliva. Reproduced with permission.^[88] Copyright 2017, John Wiley and Sons. E) A skin-integrated microneedle sensor using a novel photopatternable gel electrolyte and photopatternable skin adhesive forms a stable electrical and physical interface with the skin, enabling continuous glucose monitoring in interstitial fluids. Reproduced with permission.^[89] Copyright 2023, Elsevier. F) A fully integrated gel microneedle bioelectrode device for real-time, continuous monitoring and forecasting of biomarkers in interstitial fluids of living animals. Reproduced with permission.^[90] Copyright 2025, John Wiley and Sons.

However, tissue fluid resides in the cellular interstitial space, and obtaining it requires technical methods such as microneedles or implantable components. This introduces operational difficulties and risks, such as infection and tissue damage, and the relevant technology is still not fully developed. And most current techniques extract only 1–10 μL of tissue fluid per session, requiring several minutes to tens of minutes.^[12] Additionally, tissue fluid contains a variety of cellular metabolites, proteins, hormones, and other biomolecules, which may interfere with catalyst active sites,^[70] thereby affecting the efficiency and stability of the fuel cell.

Future progress in ISF-based GFCs will depend on advances in material selectivity, catalyst robustness, and system integration. With further technological innovation, these systems hold significant potential for powering next-generation, self-sustaining biomedical devices with minimal invasiveness.

3.3. Sweat

Sweat is increasingly used as a fuel source for GFCs. As a biofluid secreted by sweat glands in the skin,^[94,95] it can be easily collected using a collection device attached to the skin's surface, making

it especially suitable for long-term monitoring in wearable applications. This is particularly advantageous during physical activity or under conditions requiring continuous, painless sampling.

There is a correlation between glucose concentration in sweat and the body's blood glucose levels, as well as its energy metabolism status. Monitoring glucose levels in sweat can provide valuable insights into the body's metabolism. As such, sweat-based GFCs not only provide an energy source but also enable real-time, non-invasive health monitoring. While the correlation between sweat and blood glucose levels remains a topic of debate, numerous studies have suggested a strong connection between the two.^[96,97] For example, Wang et al. (Figure 7A) developed a fingertip-wearable microgrid system with the core innovation of integrating EGFCs with a stretchable AgCl-Zn cell. This system simultaneously achieves energy autonomy and multi-metabolite monitoring by passively harvesting fingertip sweat (400 glands cm^{-2}) through an osmotic hydrogel. In vivo experiments verified the system's real-time monitoring capability for postprandial glucose (+ 80 mV), providing a new paradigm for the precise health management of GFCs.^[86]

Despite these advantages, sweat-based GFCs face several limitations. Glucose concentrations in sweat are relatively low (5.6 μM to 2.2 mM),^[11] and can vary significantly across individuals

and in the same person under different physiological or environmental conditions.^[98] factors such as ambient temperature, humidity, and exercise intensity can significantly influence sweat secretion and its composition. For example, in a high-temperature environment, heavy sweating can dilute sweat, while in a low-temperature environment, sweat secretion may decrease significantly. These variations result in inconsistent glucose availability, making it difficult to achieve stable and predictable power output from sweat-based GFCs. Furthermore, such instability also affects the accuracy and reliability of glucose sensing, limiting its effectiveness for continuous and precise metabolic monitoring under certain conditions.

3.4. Tears

Tears have attracted significant attention from researchers as a promising fuel source for GFCs. Secreted naturally by the lacrimal glands, tears can be utilized in situ on the ocular surface without the need for invasive sampling, offering inherent advantages of non-invasiveness and painlessness. This makes tear-based GFCs particularly suitable for long-term, continuous monitoring applications, especially in wearable devices.

There is a clear correlation between tear glucose and blood glucose levels, so changes in tear glucose may indirectly reflect fluctuations in blood glucose levels. Based on this principle, Lee's team developed safe tear batteries integrated into contact lenses, which are recharged by biofuel during contact lens storage, providing an excellent reference for tear-based self-power (Figure 7B).^[87] This principle enables non-invasive blood glucose monitoring, which could be crucial for early diagnosis and management of diseases like diabetes. Compared with blood, tears have a simpler composition with fewer potential interferents, making tear-based glucose fuel cells more selective and accurate.

Its lower complexity, higher correlation with blood biomarkers, and properties that support accurate sensing enhance its performance in real-world applications. However, despite these advantages, tears' glucose content is much lower than that of blood, typically around 0.2 mM.^[8] Additionally, glucose concentrations in tear fluid can be influenced by factors such as emotions, environmental conditions, and ocular diseases, leading to significant fluctuations. This variability limits the output power of tear-based fuel cells, making them less stable and unable to consistently meet high power demands. Furthermore, the tear secretion rate is slow, and the amount of tears available at any given time is relatively small, with the average adult eye storing only about 6 μL .^[7] This volume is insufficient to support the high power output requirements of fuel cells over extended periods. Making it difficult to gather enough fluid to maintain the efficient operation of the fuel cell in a short timeframe. These limitations hinder the large-scale application of tears in GFCs.

Additionally, integrating GFCs into ocular platforms such as contact lenses imposes stringent requirements on the device itself. Factors such as oxygen permeability, softness, optical transparency, and wearing comfort must be carefully considered to avoid eye dryness, discomfort, or corneal damage. This places higher demands on material selection, structural design, and system integration.

3.5. Saliva

Saliva, as a physiological source of glucose, has garnered significant attention in recent years, particularly in the field of glucose testing. Its most prominent advantages are its easy accessibility and non-invasive nature. Saliva can be collected naturally or with the aid of tools, such as a collector, following simple stimulation of the salivary glands. And saliva is produced at a faster rate of about 0.3–0.4 mL min⁻¹.^[9] The collection process is painless, non-invasive, and can be done at any time or place, making it highly convenient for large-scale use. This makes saliva testing a more humane and feasible option, especially for individuals who find blood collection uncomfortable or inconvenient. Mohammadifar and Choi have investigated a low-cost, long shelf-life, and environmentally friendly micro-power source that can be easily integrated into paper-based testing devices and activated by a drop of saliva, demonstrating the feasibility of using saliva as fuel (Figure 7D).^[88]

However, the glucose concentration in saliva typically ranges from 0.028 to 0.056 mM,^[10] which is much lower than in blood. This leads to relatively limited output power from saliva-based fuel cells, making it difficult to meet the energy needs of high-power devices. Additionally, several factors such as eating, oral hygiene, and oral diseases can influence both the quantity and composition of saliva. These changes affect glucose availability and, in turn, the performance of the fuel cell. For example, after eating, saliva secretion increases significantly, but glucose concentration may decrease due to dilution. Oral infections and other diseases can lead to abnormal saliva composition, impacting the fuel cell's normal function. Moreover, saliva contains numerous bacteria and microorganisms, which may have adverse effects on critical fuel cell components such as electrodes and catalysts. These challenges need to be addressed in future studies to unlock the full potential of saliva-based glucose fuel cells.

4. Biomedical Applications

4.1. Tissue Repair

Tissue repair is a complex and delicate physiological process in the human body, and GFCs, which convert bioenergy into electrical energy, are expected to bring progress to this process. When tissue is damaged, an endogenous electric field is generated at the wound site, which acts as a directional signal to guide epithelial cells to migrate along the potential gradient to the wound bed while promoting angiogenesis and nerve growth, effectively regulating various stages of tissue repair.^[99] However, the endogenous electric field may be weak or unstable, thus making it difficult to meet the needs of tissue repair.^[100,101] In contrast, GFCs accelerate tissue repair by consuming endogenous glucose to generate electricity in situ, thereby re-establishing and strengthening the electric field that guides cell migration. This effect is particularly beneficial for diabetic wounds, as GFCs can also reduce local blood glucose levels in the wound area. For example, Fan's team investigated a self-powered enzyme-linked microneedle patch that reduces local blood glucose in diabetic wounds through a cascade reaction of GOx at the anode and HPR at the cathode, generating microcurrents that synergize to achieve antimicrobial, anti-inflammatory, and bioelectrical stimulation, and

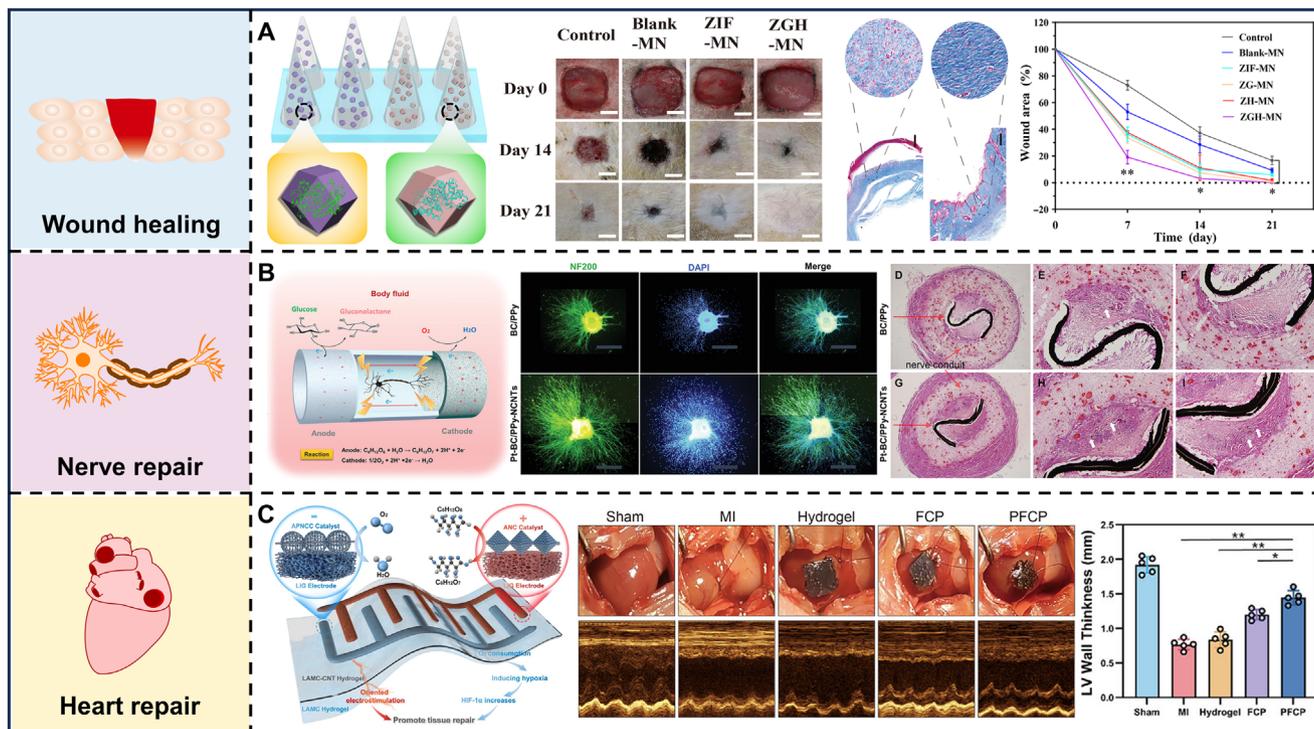


Figure 8. GFCs for tissue repair applications. A) GFCs can effectively reduce local hyperglycemia in diabetic wounds while generating stable microcurrents that promote healing. Reproduced with permission.^[102] Copyright 2023, Open Access. B) A novel self-powered electrical stimulation neural scaffold that facilitates nerve repair. Reproduced with permission.^[105] Copyright 2019, John Wiley and Sons. C) Flexible patterned fuel cell patches that stimulate myocardial restoration. Reproduced with permission.^[106] Copyright 2025, John Wiley and Sons.

the ZGH-MN group, which used the microneedle patch, achieved a wound area of 0% by day 21 compared to the control group and the other treatment groups, demonstrating rapid, complete and prevented scar formation healing effect (Figure 8A).^[102] In addition, Zhang et al.^[103] invented a patch for GFCs, which consists of a MAF-7-protected GOx/HPR anode and a HPR enzyme cathode. The patch can utilize hyperglycemia as a fuel to generate electricity and generate large amounts of reactive oxygen species (ROS) in situ to synergistically regulate local hyperglycemia and break the low H_2O_2 limitation. In in vivo experiments, wounds in diabetic mice treated with the patch eliminated inflammation and formed mature skin with new hair follicles within 10 days, showing its great potential for treating bacterially infected diabetic wounds. Similarly, the CPAN-AMP4 hydrogel developed by Guo's team is based on the GFCs principle, which mimics an enzymatic cascade reaction by depositing Au nanoparticles on the surface of MoS_2 nano-enzymes, generating antimicrobial ROS and regulating blood glucose during hyperglycemia, and inhibiting insulin release by switching the enzyme activity after blood glucose returns to normal, ultimately leading to almost complete closure of diabetic mouse wounds in 21 days, with a repair rate that is three times faster than that of commercial dressings.^[104]

And, based on the different requirements for electrical stimulation modes during various types of tissue repair, researchers have developed different types of glucose fuel cell patches. For example, Zheng's team invented a tubular GFC self-powered electrically stimulated multi-block conductive neural scaffold.^[105] The scaffold is based on bacterial cellulose, and the conductive

substrate was prepared by in situ polymerization of pyrrole and electrodeposition of platinum nanoparticles on the anode side to catalyze glucose oxidation and loading of N-CNTs on the cathode side to promote oxygen reduction. This self-powered neural scaffold significantly promoted rat sciatic nerve regeneration in in vivo experiments, resulting in denser and more ordered regenerated nerve fibers with thickened axons and myelin sheaths, while sciatic nerve function indexes at 8 and 12 weeks postoperatively showed better motor function recovery than the control group (Figure 8B). Moreover, Wang et al.^[106] invented flexible patterned fuel cell patches (PFCP) for myocardial tissue repair. The patch uses PtNi nanochains and PtNi nanocages as electrocatalysts to catalyze glucose oxidation and oxygen reduction reactions. PFCP can reconstruct the electrophysiological environment by simulating the endogenous electric field of myocardium, inhibiting fibrosis, and promoting angiogenesis. In the rat myocardial infarction model, after 4 weeks, its ejection fraction reached $69.456 \pm 0.69\%$, and the left ventricular end-diastolic volume was only $434.0 \pm 53.0 \mu L$, which was significantly better than other groups, and the myocardial tissue was close to normal state. The vascular density and key protein expression were significantly increased, indicating that it can effectively repair the infarcted myocardium (Figure 8C).

GFCs innovatively combine the endogenous substances of living organisms with electrical stimulation technology, which not only provides precise energy support, but also promotes tissue regeneration by modulating the local microenvironment.^[99] Recently, researchers have made remarkable progress in nerve

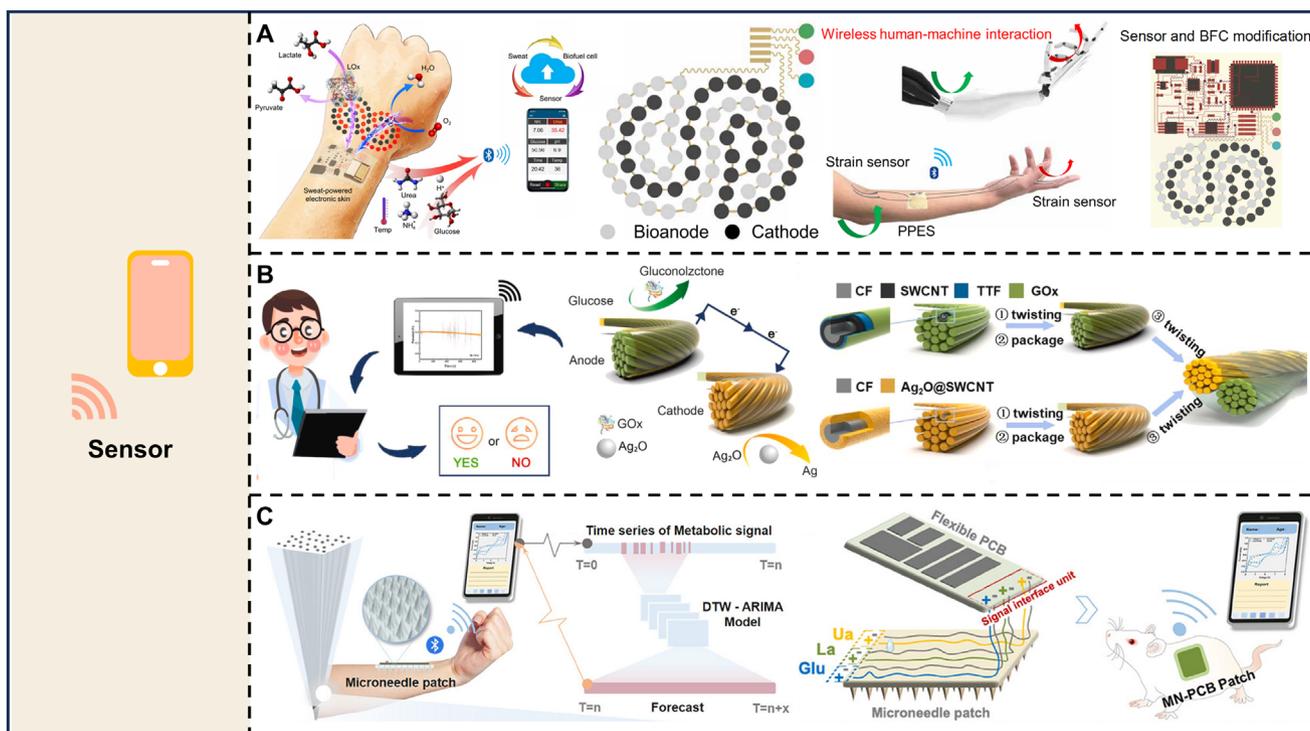


Figure 9. GFCs for biosensing applications. A) A flexible, fully perspiration-powered integrated electronic skin for in situ multiplexed metabolic sensing. Reproduced with permission.^[122] Copyright 2020, The American Association for the Advancement of Science. B) A self-powered biosensing suture based on biofuel cells for accurate glucose concentration monitoring at the wound site. Reproduced with permission.^[123] Copyright 2024, Elsevier. C) A fully integrated gel microneedle biosensing device for real-time, continuous monitoring and forecasting of biomarkers in interstitial fluids of living organisms. Reproduced with permission.^[90] Copyright 2025, John Wiley and Sons.

repair^[107,108] and bone repair^[109,110] methods by modulating the microenvironment, and GFCs, as a typical representative in the field of self-powered energy, have opened up a brand-new pathway for tissue repair. The successful application of GFCs for multi-tissue repair from skin wounds to nerves and myocardium has proved their adaptability and versatility in complex physiological environments. Its biocompatibility and energy self-sufficiency make it expected to become an important tool in the field of tissue repair therapy.

4.2. Biosensor

Accurate and rapid monitoring of glucose concentration in blood is of vital importance for the prevention, diagnosis, and treatment of diabetes.^[111,112] Diabetes is a typical chronic disease caused by metabolic disorders,^[113] characterized by abnormally elevated blood glucose levels and is often accompanied by serious complications such as diabetic foot ulcers and nephropathy.^[114–116] When fasting, the normal blood glucose concentration should be between 3.9 and 5.6 mM, and both hypoglycemic and hyperglycemic conditions may trigger adverse consequences. In view of this, the development of an accurate and rapid glucose detection method is particularly urgent for health monitoring and clinical diagnosis. GFC biosensors offer an ideal solution to meet this demand. These sensors utilize enzymes or other catalysts to oxidize glucose, releasing electrons and generating an electrical

signal (e.g., voltage, current, or power) that has a deterministic functional relationship with glucose concentration. This technology promises to enable self-powered, real-time, and continuous glucose monitoring.

However, there is still much room for improvement in the sensitivity, selectivity, and stability of currently available glucose sensors.^[117] Among many testing methods, optical analysis is regarded as the “gold standard” for blood glucose measurement because of its excellent accuracy, providing a solid and reliable basis for clinical diagnosis.^[118] The principle of this method is based on photoelectric colorimetry, which accurately determines glucose concentration by detecting color changes during enzymatic reactions. However, its time-consuming nature and high reliance on specialized equipment have severely limited its widespread use in home environments.

In contrast, electrochemical detection methods, especially in the field of wearable microsensors,^[119] have received much attention in recent years due to their significant advantages such as high sensitivity, high selectivity, low cost, and ease of operation.^[120,121] For example, Gao’s team investigated a flexible, fully perspiration-powered integrated electronic skin for in situ multiplexed metabolic sensing (Figure 9A).^[122]

Continuous glucose monitoring is of irreplaceable value for dynamic tracking and effective management of blood glucose levels, and implantable glucose sensors are a key technological tool to achieve this goal. Nevertheless, due to biocompatibility issues such as biological contamination and decreasing enzyme

activity over time, the performance of the sensors tends to gradually deteriorate after implantation in the human body or even fail completely in some cases. To address this challenge, researchers have developed anti-bio-contamination^[124] and enzyme immobilization techniques^[125] to enhance the long-term stability of the sensors.

It is worth noting that most of the current blood glucose monitoring devices still rely on blood samples for testing, which undoubtedly increases the pain and brings inconvenience to patients. While, Hu's team developed a self-powered biosensing suture, with the innovation lying in the integration of GFC into the suture structure. This integration allows the suture to directly reflect the glucose concentration of the wound through changes in open-circuit voltage. Fourteen-day experiments confirmed that its healing effect is comparable to that of traditional sutures and is biocompatible, providing a minimally invasive and intelligent monitoring solution to reduce the risk of chronic wounds (Figure 9B).^[123]

At the same time, to minimize monitoring trauma, the development of non-invasive or minimally invasive glucose detection technologies for body fluids such as sweat,^[126] tears,^[127] and saliva^[128] has become an important research direction in biosensor. With the rapid development of advanced flexible materials and fabrication technologies, it has become possible to design wearable devices for real-time monitoring, which will greatly improve the quality of life for patients. Many research teams have successfully demonstrated the feasibility of wearable patches to monitor diabetes by detecting glucose concentration in tears,^[127] sweat,^[129] and saliva.^[130]

However, these external body fluids are highly susceptible to environmental factors such as lag time, low sample content, and poor reproducibility.^[131] In addition, accurately establishing the correlation between the glucose concentration measured in these body fluids and the actual blood glucose value has become a key challenge for researchers to address.

4.3. Drug Delivery

With the continuous development of stimulus-responsive materials and technologies, drug release modulation can now be achieved through various external or internal stimuli. Among these, electrical stimulation shows great potential due to its ease of integration with sensors or microchips and its ability to provide precise temporal and spatial control of release.^[132] Furthermore, with the rapid advancement of self-powered devices, the self-powered performance of electrical stimulation has garnered increasing attention. Glucose fuel cells, as a representative of self-powered devices, have gained significant focus in drug delivery due to their unique innovativeness and considerable medical potential.

Specifically, GFCs convert the chemical energy of blood glucose into microcurrents that drive the targeted transmembrane release of charged drugs through ion import and electroosmosis mechanisms. This process is expected to establish a negative feedback loop linking blood glucose concentration, electrical activity, and drug delivery.

Ramón Martínez-Máñez et al.^[133] studied a glucose-driven gated nanomotor, which integrates a quadruple mechanism of

autonomous motility (glucose \rightarrow H₂O₂ \rightarrow O₂ propulsion). The nanomotor showed significant deep penetration and anti-tumor effects in cells, 3D spheres, mouse models (early/advanced tumors), and patient-derived organs (Figure 10A). The innovation of this nanomotor lies in solving the two major bottlenecks of conventional nanomotors: biofuel toxicity and targeted drug release control. It provides a synergistic therapeutic platform for exogenous, power-free treatment of solid tumors.

In addition, Prof. Edmond Magner's team developed a self-powered drug release system using an EGFC. The bioanode (GOx/Os polymer) oxidizes glucose, while the biocathode (BOD/Os polymer) reduces O₂, driving the conducting polymer (PEDOT/PPy) to achieve controlled drug release.^[134] In a physiological environment, the system efficiently releases both anionic and cationic drugs through precise voltage regulation. The switching ratio of FLU can reach 18 times. The in-situ release and nuclear staining of DAPI were verified in cell culture experiments (Figure 10B). This technology eliminates the dependence of traditional implantable devices on external power sources, offering a new strategy for precise, on-demand drug delivery.

Moreover, Zhu et al.^[135] extended the application of self-powered biosensors to drug delivery by successfully integrating a glucose/O₂ fuel cell-based biosensor with a targeted drug delivery system, creating a model with self-diagnostic and self-assessment capabilities. This study provides valuable insights for clinical cancer therapy.

With the ongoing exploration and application of GFCs in drug delivery, their technological advantages have become increasingly prominent, opening new possibilities for precision medicine. In the future, this innovative technology is expected to be deeply integrated with intelligent diagnosis and treatment systems, dynamically regulating drug release through real-time monitoring of physiological data and enabling truly personalized treatment. Meanwhile, its wide application in wearable and implantable medical devices will further expand the scope of medical scenarios, overcoming the time and space limitations of traditional treatments.

4.4. Energy Supply

GFCs, as an emerging biomedical energy supply technology, overcome traditional energy limitations through their unique energy supply mechanism. They directly convert the chemical energy of glucose into electrical energy, achieving precise and efficient energy utilization. Specifically, during the electrochemical oxidation of glucose at the anode, both electrons and protons are released. The electrons flow through the external circuit to perform work, while the protons migrate through the electrolyte to the cathode, where they react with reduced oxygen to form water. This cyclic process enables the continuous conversion of chemical energy into electrical energy, ensuring a stable power output.

In the field of smart contact lenses,^[136] the fully embedded glucose fuel cell holds potential as a non-invasive medical device or for virtual displays (Figure 11A). The fuel cell is safe, flexible, and durable, capable of being stored for weeks while providing stable power. When exposed to a 0.05 mM glucose solution, the optimized module chemistry and porous structure achieved a steady-state maximum power density of 4.4 $\mu\text{W cm}^{-2}$, maintaining

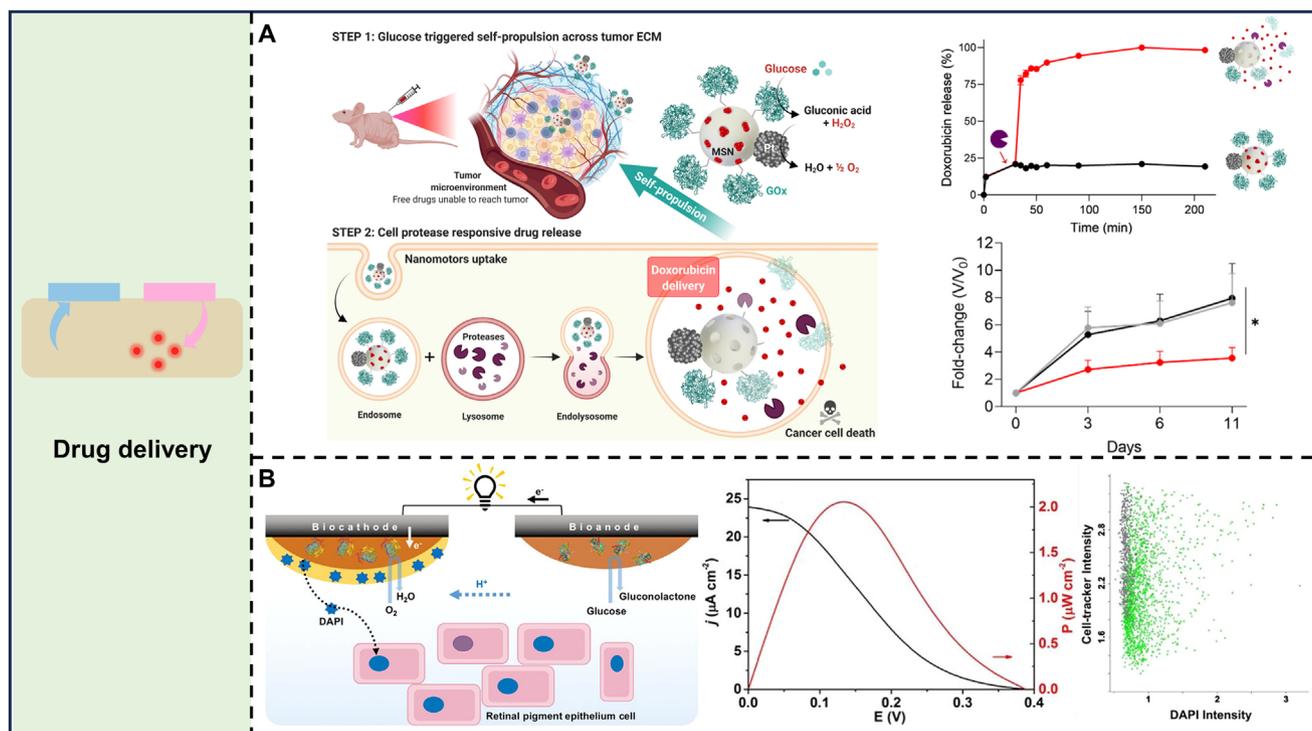


Figure 10. GFCs for drug delivery. A) A glucose-driven gated Janus nanomotor for on-demand anticancer drug delivery in the treatment of solid tumors. Reproduced with permission.^[133] Copyright 2020, Open Access. B) An osmium redox conductive polymer (CP) mediated EGFC, with a CP-drug layer on the cathode, facilitates the rapid release of model drug compounds during discharge in the presence of glucose and dioxygen. Reproduced with permission.^[134] Copyright 2020, American Chemical Society.

performance even after 100 bending cycles. When connected to an electrically responsive hydrogel capacitor, it was able to differentiate between normal and diabetic tear glucose levels, which is significant for diabetes monitoring.

In the field of implantable medical devices, Chung et al.^[137] pioneered the first pigeon implantable EGFCs and brain stimulator integrated system. This system achieved a 0.08 mW power output, which, when combined with a booster circuit, collected 28.4 mJ of energy to drive wireless neurostimulation. This breakthrough opens new possibilities for self-sustaining neuromodulation in living birds (Figure 11B).

Additionally, Evgeny Katz's team modified the anode and cathode of biocatalytic electrodes made from buckypaper into PQQ-dependent glucose dehydrogenase and laccase, respectively.^[138] These were assembled into a flow biofuel cell filled with serum solution, mimicking the human blood circulation system. It can be activated to power a pacemaker by adjusting the voltage to the desired value using a charge pump and DC–DC converter interface circuit. The continuous operation of the pacemaker represents the first demonstration of physiologically generated electrical energy to activate a pacemaker (Figure 11C). This innovation holds promise for future body-powered electronic implantable medical devices.

GFCs, with the unique ability to convert endogenous glucose into electricity, show great potential in the energy supply of medical devices, offering new possibilities for the development of wearable and implantable technologies. Currently, bottlenecks in energy conversion efficiency, service life, and biocompatibility are

being gradually overcome through continuous breakthroughs in material science.^[139] In the future, glucose fuel cells are expected to play a key role in the energy supply of medical equipment.

5. Conclusion and Perspectives

In this review, we provide a comprehensive and in-depth overview of the research progress on GFCs. Based on catalyst type and electrode structure, we categorize GFCs into four types: i) MGFC, ii) EGFC, iii) AGFC, and iv) HGFC. For each type of GFC, we describe its multidimensional applications in biomedical fields, including tissue repair, biosensing, drug delivery, and energy supply. Overall, GFC technology has shown positive development and great potential, with promising application prospects. It is expected to provide solid theoretical support and innovative ideas for the future expansion of GFC applications in biomedical fields, laying a meaningful and solid foundation for realizing the deeper development of GFCs. However, despite its unlimited development potential in biomedical applications, GFC technology still faces many challenges that need to be addressed at this stage. **Figure 12**

5.1. Miniaturization

In the future, the miniaturization of GFCs is expected to achieve significant breakthroughs, particularly at the micro- and

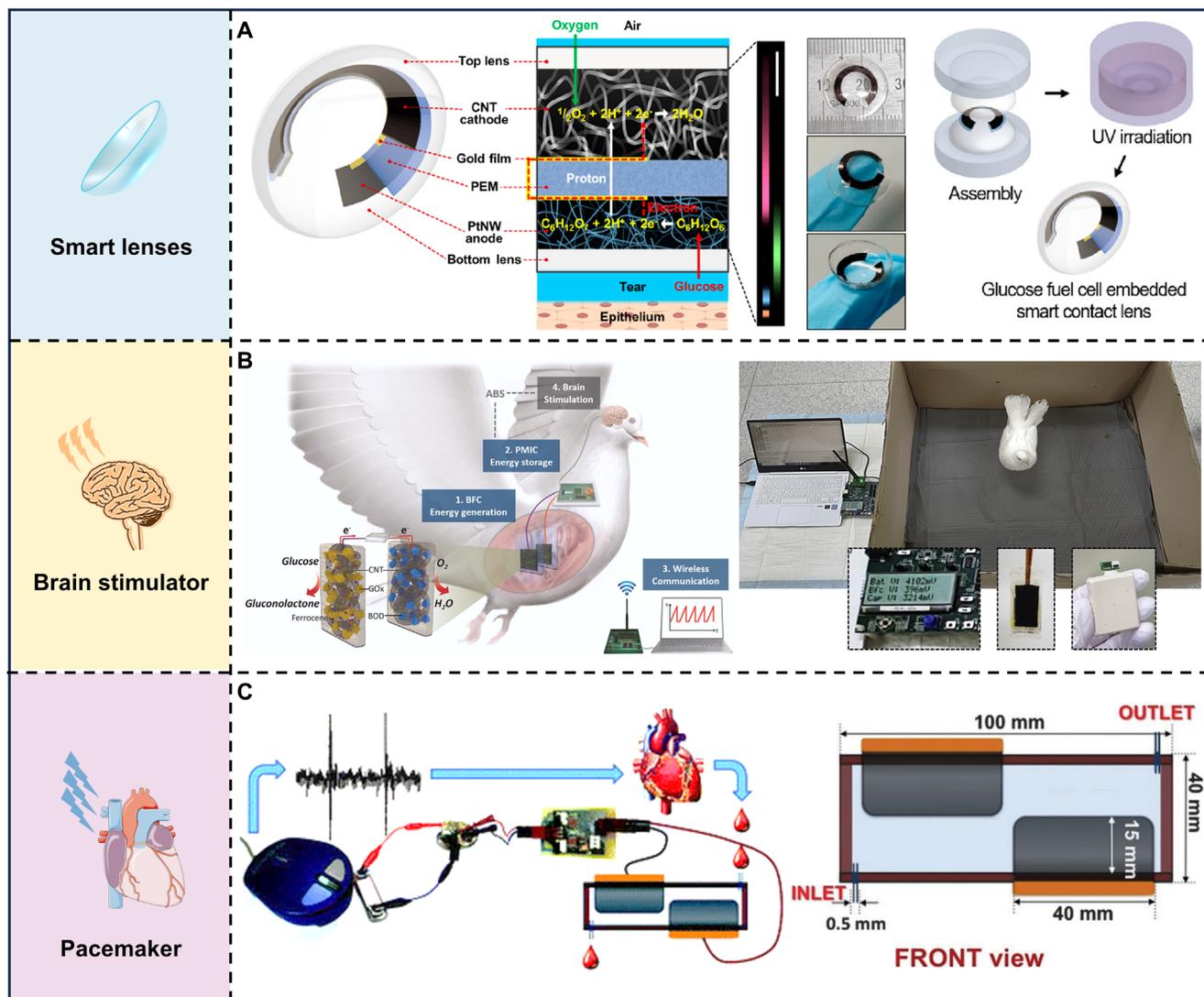


Figure 11. GFCs for powering biomedical devices. A) Smart contact lenses with fully embedded glucose fuel cells, which produce stable power throughout the day or during intermittent use after storage for weeks. Reproduced with permission.^[136] Copyright 2022, American Chemical Society. B) An integrated GFC and brain stimulator, with the GFC supplying power to the brain stimulator. Reproduced with permission.^[137] Copyright 2020, Elsevier. C) GFC powers a pacemaker, simulating the human blood circulatory system. Reproduced with permission.^[138] Copyright 2013, The Royal Society of Chemistry.

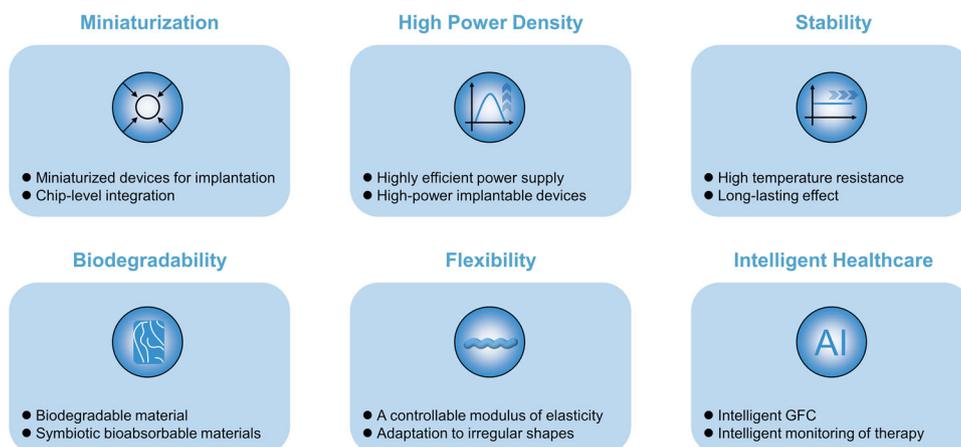


Figure 12. Key challenges and considerations of GFCs for biomedical applications.

nanoscale, greatly enhancing their potential in the biomedical field.^[24] With the help of nanomaterials, thin-film technologies, and advanced microfabrication processes, GFCs will be able to deliver excellent energy output and stability within very small volumes. At the same time, chip-scale integration technology will allow for the seamless integration of GFCs with electronic chips, sensors, and other components, creating a miniaturized, high-efficiency system-on-chip.^[140] This not only optimizes energy management but also enables real-time monitoring and feedback on both the working status of the GFCs and human physiological parameters. Through chip-level integration, GFCs will provide long-term, stable energy support for implantable medical devices such as pacemakers and neurostimulators, as well as wearable medical devices like health monitoring devices. This will significantly enhance the performance of these devices and improve the overall patient experience.

5.2. High Power Density

Furthermore, improving the power density of GFCs is crucial, as it enables these cells to power higher-demand implantable devices, thereby expanding their range of applications.^[141] Currently, researchers are focusing on optimizing GFC performance through several approaches. From a material and structural standpoint, using nanomaterials, composites, and 3D structural designs can significantly increase the specific surface area of the electrodes. This enhancement improves catalytic efficiency and accelerates the mass transfer of reactants, providing a foundation for boosting power density. Simultaneously, improving the catalyst plays a key role. On one hand, exploring non-platinum catalysts can reduce costs and broaden the selection range. On the other hand, optimizing the immobilization method of enzyme catalysts is essential to enhance their stability and activity, further improving GFC power density. Energy management and control strategies should also be a priority. An intelligent energy management system can effectively allocate energy storage and release based on the equipment's operating status and needs. Power regulation technologies will ensure the stability and high efficiency of energy output, allowing it to meet the diverse power demands of different devices. Additionally, surface modification of electrodes and ongoing optimization of the overall structural design can enhance GFC performance. By combining these innovative strategies, GFCs are expected to become an ideal energy source for high-power implantable devices in the future. This will enable efficient *in vivo* energy supply and contribute significantly to technological advancements in medical and other fields.

5.3. Stability

As technology continues to advance, implantable GFCs are becoming a reality. However, this advancement goes beyond simply ensuring the long-lasting output of GFCs. These devices must also demonstrate excellent thermal stability,^[24,142] a critical performance characteristic. Prior to implantation into the human body, GFCs undergo a rigorous thermal sterilization process to minimize any potential adverse effects on the body after implantation and to ensure ideal biocompatibility with hu-

man tissues. Moreover, the long-term stable output characteristics of GFCs open up broader prospects in the field of implantable and wearable medical devices. Only with good thermal stability can GFCs withstand the sterilization process without damage, ensuring they are able to enter the body smoothly and function properly. Their stable output can then meet the continuous energy demands of implantable and wearable medical devices. Several *in vivo* experiments have further validated its durability and biocompatibility, demonstrating stable electrical output and minimal inflammatory response during prolonged implantation. These findings provide crucial evidence supporting the translational feasibility of GFCs for future biomedical applications.^[18,106,143] This will ultimately promote these devices in better serving human health, driving more innovations and breakthroughs in healthcare.

5.4. Biodegradability

At the same time, the development of composite materials with biodegradable^[144] and symbiotic bioabsorbable is advancing the production of GFCs. Biodegradability is defined as the capability of a substance to be naturally broken down and metabolized by organisms in the environment or within a living body.^[145] Symbiotic bioabsorbable materials and electronic devices degrade within biological systems via processes like material hydrolysis and bodily metabolic reactions.^[145,146] The symbiotic relationship is formed through the direct conversion of these degradable materials into nutrients for cells, tissues, and the body, thus eliminating the need for equipment retention. By using chemical modifications or composite nanomaterials, GFCs can be endowed with these properties. These properties allow GFCs to be absorbed by the human body after completing their function, reducing the risks and discomfort associated with secondary surgeries.^[145] Absorbable materials enhance the biocompatibility of GFCs, making them more acceptable to the human body and minimizing adverse reactions. This enhances the overall performance of the GFC. The combination of these innovations is expected to greatly contribute to the advancement of glucose fuel cells in biomedical applications.

5.5. Flexibility

Moreover, considering that GFCs are expected to be used in human wearable and implantable applications in the future, their design must strictly adhere to ergonomic principles. To adapt to the complex and changing surfaces of different parts of the human body, GFCs need to possess sufficient flexibility and a controllable modulus of elasticity.^[147] This bio-conformity requires the material to adapt to the irregular shapes of human tissues while also ensuring comfort during use.^[148] Moreover, the flexible design promotes integrated packaging of functional modules. Compared to rigid components, flexible substrates make it easier to achieve all-in-one designs. It is worth noting that the modulus of flexible substrate materials (e.g., hydrogels,^[149] fabrics^[150,151]) is typically much lower than that of human tissues, which improves biocompatibility but may reduce power generation efficiency due to interfacial coupling effects. Future research should

focus on developing flexible material systems that match the biomodulus of tissues while maintaining high electromechanical conversion efficiency. Overcoming the trade-off between flexibility and high performance can be achieved through various approaches, such as composite structure design^[152,153] and interface energy level regulation.^[143] Establishing design guidelines for GFCs based on the synergistic optimization of materials, structures, and functions will provide valuable theoretical support for the clinical translation of GFC technologies.

5.6. Intelligent Healthcare

In the field of smart healthcare, the integration of GFCs and artificial intelligence (AI) can further optimize their use in biomedicine. AI excels at processing and analyzing large volumes of complex data, making predictions and classifications based on this information.^[154] By combining GFCs and AI, intelligent monitoring and diagnosis become possible, with GFCs providing energy to monitoring equipment. These devices can then collect and transmit real-time physiological data to the AI system, which analyzes the data to detect abnormalities, offering a foundation for early diagnosis and treatment of diseases. Additionally, AI can play a key role in formulating personalized treatment plans. By analyzing a patient's physiological data, medical history, and GFC monitoring information, AI can create tailored treatment plans.^[155] It can also adjust these plans in real time based on ongoing monitoring data, ensuring optimal therapeutic outcomes.

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Conflict of Interest

The authors declare no conflict of interest.

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