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Perspective

The direct use of enzymatic biofuel cells as functional bioelectronics

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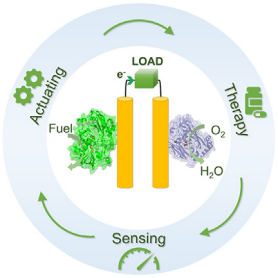
HIGHLIGHTS

- The direct use of enzymatic biofuel cells (EBFCs) as bioelectronics is reviewed.
- EBFC can enable instrument-free self-powered biosensing.
- EBFC can enable autonomous pulse generation.
- The direct use of EBFC leads to various therapeutic systems.

GRAPHICAL ABSTRACT



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ABSTRACT

Enzymatic biofuel cells (EBFCs) are a subgroup of fuel cells that use enzymes as catalysts. EBFCs that utilize physiological substrates such as glucose or lactate are of great interest as implantable or wearable power sources to activate medical devices. This contribution introduces the working principles of EBFCs and summarizes recent progress in EBFC-enabled biosensors, pulse generators, and therapy. Biosensors with self-powered characteristic enjoy high selectivity, leading to potential "instrument-free" or "expensive-instrument-free" measurement. Autonomous pulse generation is based on the hybrid of EBFC and supercapacitor, which is promising for the application in medical related electrostimulation. By providing the direct electrical stimulation, or controllably releasing drug, EBFCs can also be used for self-powered therapeutic system. The further combination of self-powered sensing and treating enables EBFC as a possible platform of diagnostics and therapeutics. Future efforts can be focused on resolving the limited power density and lifetime of EBFC.

1. Introduction

Enzymatic biofuel cells (EBFCs) are a type of electrochemical device for converting chemical energy into electricity (Fig. 1) [1,2]. As a subgroup of fuel cells, EBFCs rely on the utilization of enzymes as their catalysts, governing fuel oxidation at the anode and typical dioxygen reduction at the cathode. The unique features of enzymes mean EBFCs offer several new properties, making them distinctive from conventional fuel cells: (i) The enzymes are selective and generally immobilized on the electrodes, so membranes are not needed to separate the anolyte and catholyte, which simplifies the cell configuration and makes miniaturization easier. (ii) EBFCs can operate in mild conditions, i.e., physiological temperature and pH. (iii) The large library of enzymes in nature enables a wide range of possible fuels, such as sugars, biomass, and even inorganic ions [3].

The first documented EBFC appeared in 1964, prepared by Yahiro et al. It utilized a glucose oxidase (GOx) bioanode that underwent the two-electron oxidation of glucose into gluconolactone, and an abiotic Pt cathode [4], yielding a glucose/O_2 EBFC. Implantable glucose/O_2 fuel cells that consume blood glucose to activate implanted electronics have

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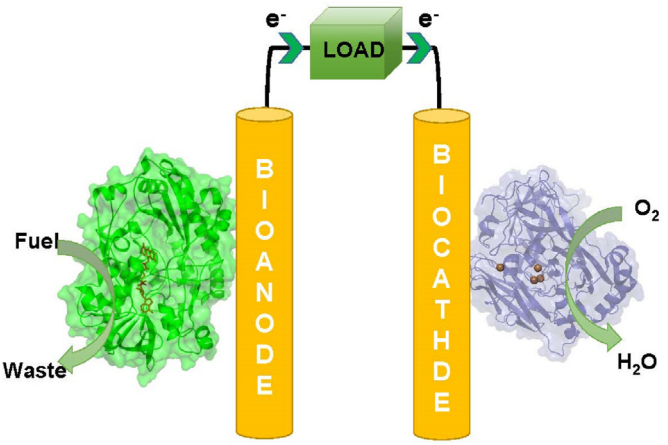

Fig. 1. Schematic drawing of an EBFC, consisting of a GOx-based bioanode (PDB: 3QVP) and a BOx-based biocathode (PDB: 2XLL).

drawn tremendous research interest since the 1960s [5], and it is not surprising that the application of a glucose/O_2 EBFC as a potential implantable power supplier was demonstrated in the early 2000s [6–8]. Recent years have seen the emergence of noninvasive types, especially lactate/O_2 EBFCs [9,10], which are envisioned as promising power suppliers for wearable electronics [11,12]. Aside from H_2/O_2 EBFCs, EBFCs are associated with small-volume, low-weight medical bioelectronics rather than large-scale, cheap electricity production [13].

Bioelectronics are artificial devices/machines that are either implantable within or wearable on the body, offering novel opportunities for personalized medicine with respect to sensing, diagnosis, and treatment. These bioelectronics pose heavy demands on miniaturized power units, and the next generation of them should be biodegradable. But current state-of-the-art batteries are bulky (for instance, occupying three quarters of the total volume of a subcutaneously implanted pacemaker), heavy, must be well sealed, and require surgical removal when they fail.

Glucose/O_2 EBFCs have been proposed to replace the primary lithium iodide battery [14] in a pacemaker (Fig. 2a), but there is a mismatch between the maximum output voltage generated by a single glucose/O_2 EBFC (thermodynamically 1.19 V for two-electron glucose oxidation [2]) and the required input voltage for mainstream bioelectronics (typically at least 3 V for a pacemaker) [13]. Series connection of multiple EBFCs is not feasible in vivo due to ionic short-circuiting, as they share the same electrolyte [15]. An external voltage booster can be adapted to amplify the output voltage of a single EBFC to activate a pacemaker [16] or a brain stimulator [17] (Fig. 2), but this increases the total volume of the power unit and consumes extra power generated by the EBFC. In practice, the interface between EBFCs and bioelectronics will inevitably bring further challenges. An alternative is the emerging innovative "self-powered" approach [18–22], in which the direct use of EBFCs for functional bioelectronics would eliminate the EBFC/bioelectronic interface.

Although numerous reviews have been published on the use of EBFCs for implantable and wearable devices [5,11,23–26], few focus is on the direct use of enzymatic biofuel cells as functional bioelectronics [18,22]. In the present contribution, the author first describes the fundamental elements of EBFCs and then briefly summarizes the key aspects of this rapidly growing research area. Special attention is devoted to EBFC-enabled self-powered biosensors, pulse generators, and therapies. Finally, suggestions and perspectives are offered with the aim of opening up new possibilities for EBFC-based bioelectronics.

2. Fundamentals of enzymatic biofuel cells

2.1. Electron transfer

An EBFC is assembled with two bioelectrodes (Fig. 1), which harness the electron transfer (ET) route of oxidoreductases. Enzymes are macro biomolecules (typically several nm in size) 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. To reset the redox status of the catalytic center for the next cycle of biocatalysis, nature uses an electron acceptor (e.g., dioxygen for GOx) or donor (e.g., bilirubin for bilirubin oxidase (BOx), a common oxygen-reducing enzyme). In bioelectrochemistry, inorganic electrodes are used to manipulate external electrons, thereby serving as the artificial electron acceptor/donor for the enzyme (Fig. 3). According to quantum mechanical ET theory, the ET rate decreases exponentially with the electron tunneling distance [27], and an upper threshold of 1.5 nm is required for feasible ET [28,29].

There are two types of ET mechanisms in enzymatic bioelectrochemistry: direct (DET) and mediated (MET). DET occurs only when the catalytic center or the built-in ET relay of the enzyme (such as hemes) is close enough to the electrode within the threshold electron tunneling distance [30]. Taking BOx 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 (Fig. 3a). T1 Cu, communicating with the trinuclear cluster by means of intramolecular ET, is located a short distance from the protein surface, permitting rapid DET [31]. In contrast, another common enzyme, GOx, purified from *Aspergillus niger*, contains a flavin active center located at least 1.7 nm away from the protein surface [32], making DET impossible. Artificial redox molecules, i.e., mediators [33–35], including quinone compounds and transition-metal complexes, among others, have been developed to exchange electrons with GOx, leading to MET (Fig. 3b).

2.2. Enzyme immobilization

Enzyme immobilization is crucial for practical EBFCs to accommodate enzymes on the electrode surface, allowing cell simplification, enhanced operational stability, and control over the ET process [36]. General methods of enzyme immobilization, from weak to strong, are physical adsorption, polymer entrapment, affinity and covalent binding, and cross-linking [2]. The enzyme should be steadily integrated on the electrode, maintaining its structural integrity and conformational flexibility, and thereby its catalytic activity. These factors are determined by the immobilization method, and there is as yet no perfect immobilization strategy to meet all the requirements. In addition, strong immobilization can prevent enzyme detachment, cause irreversible enzyme deactivation, or lead to decreased activity due to the loss of conformational freedom. DET, where the enzyme's orientation plays a governing role, is specifically sensitive to the electrode modification method [37–39]. The surface should accommodate a DET-capable enzyme in a proper orientation, with its redox/catalytic center as close to the electrode surface as possible. Electrode materials, which should be at least electronically conductive, are shifting from smooth surfaces to high-surface-area nanomaterials, such as carbon nanotubes (CNTs) [39,40], graphene [3,41,42], gold nanoparticles (AuNPs) [43], and nanoporous gold (NPG) [44], among others. Novel properties have been achieved through the introduction of nanomaterials, including enhanced enzyme loading and the promotion of enzyme orientation and stability [37]. New nanomaterials could bring more possibilities for enzymatic bioelectrodes, and thus for EBFCs.

2.3. Performance parameters of enzymatic biofuel cells

An EBFC is an energy harvester, permitting continuous discharge when connected to a load in the presence of fuel and oxidant. It can be discharged in a two-electrode system by various electrochemical techniques, including amperometric, voltammetric, and galvanostatic [45], resulting in a polarization curve and the corresponding power density profile (Figs. 4a–b). Important parameters are open circuit voltage (OCV), maximum power density (P_{max}), and maximum current density (Figs. 4a–b).

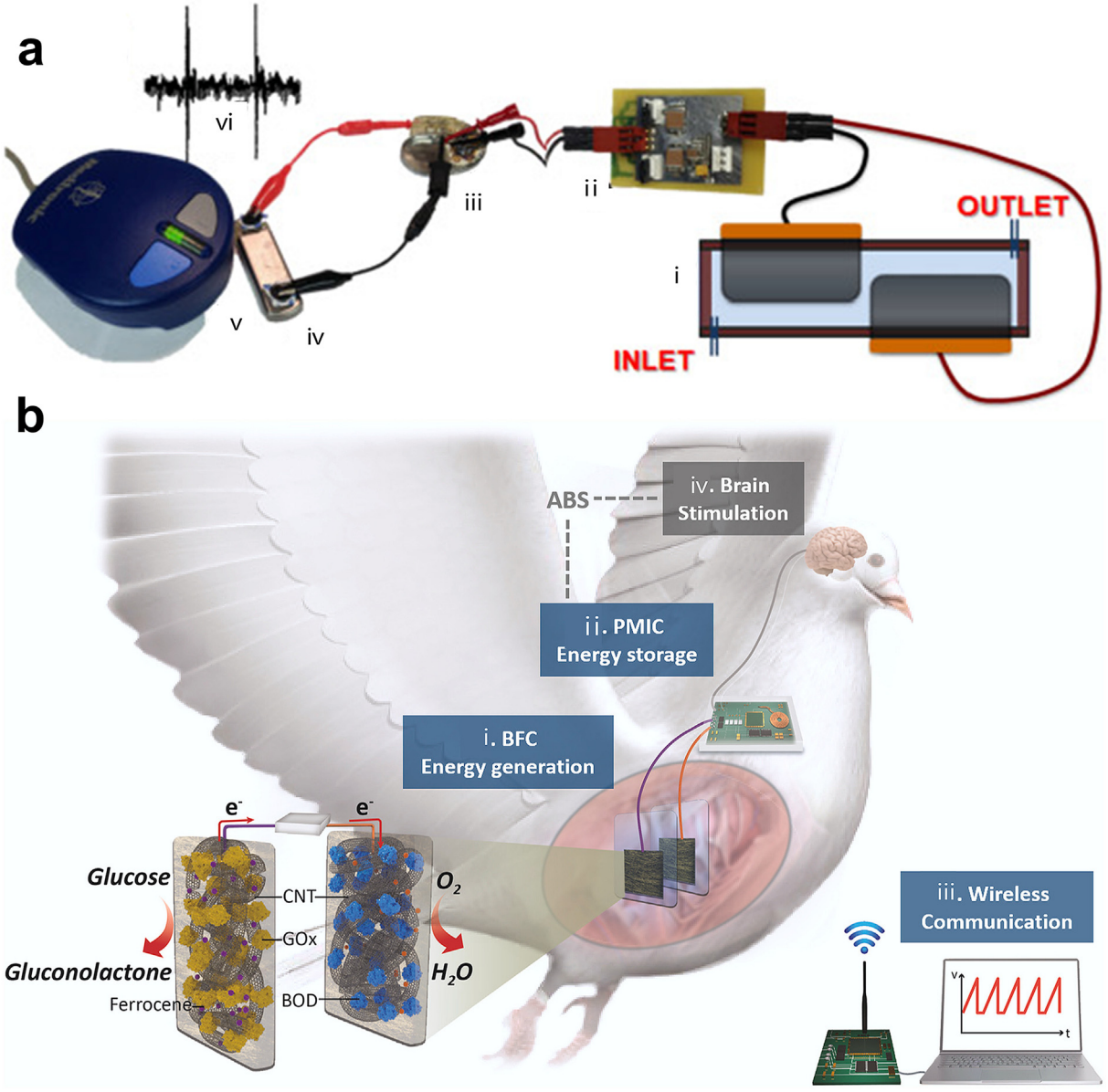

Fig. 2. (a) The application of (i) a single EBFC to power (iii) a pacemaker. A voltage booster (ii) is used to increase the output voltage of the EBFC. The pacemaker performance evaluation section comprises (iv) an implantable loop recorder, and (v) a sensor device; (vi) shows the registered pulse signals generated by the pacemaker (iii). An electrode with a geometric area of 6 cm^2 is adopted to operate the voltage booster, which is, however, too large for implantation. Adapted from Ref. [16] with modification and permission. (b) Implantation of an EBFC and a brain stimulator in a pigeon. The power harvested by the EBFC is manipulated by the power management circuit via wireless communication. Adapted from Ref. [17] with permission.

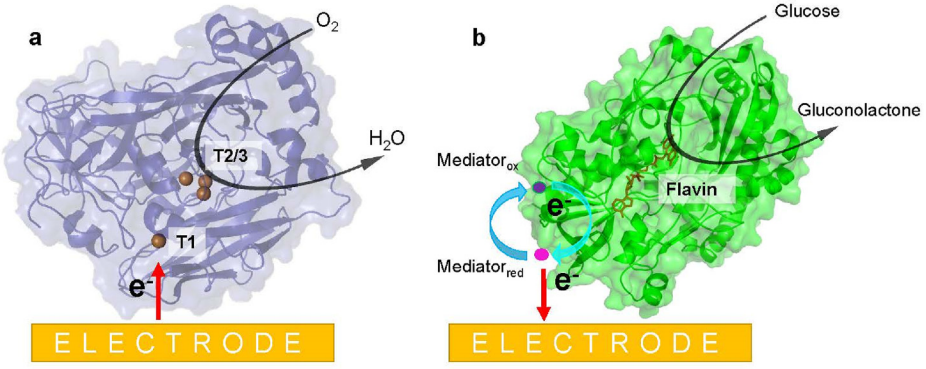

Fig. 3. Schematic drawing of (a) the DET of BOx (PDB: 2XLL) and (b) the MET of GOx (PDB: 3QVP) on an electrode surface.

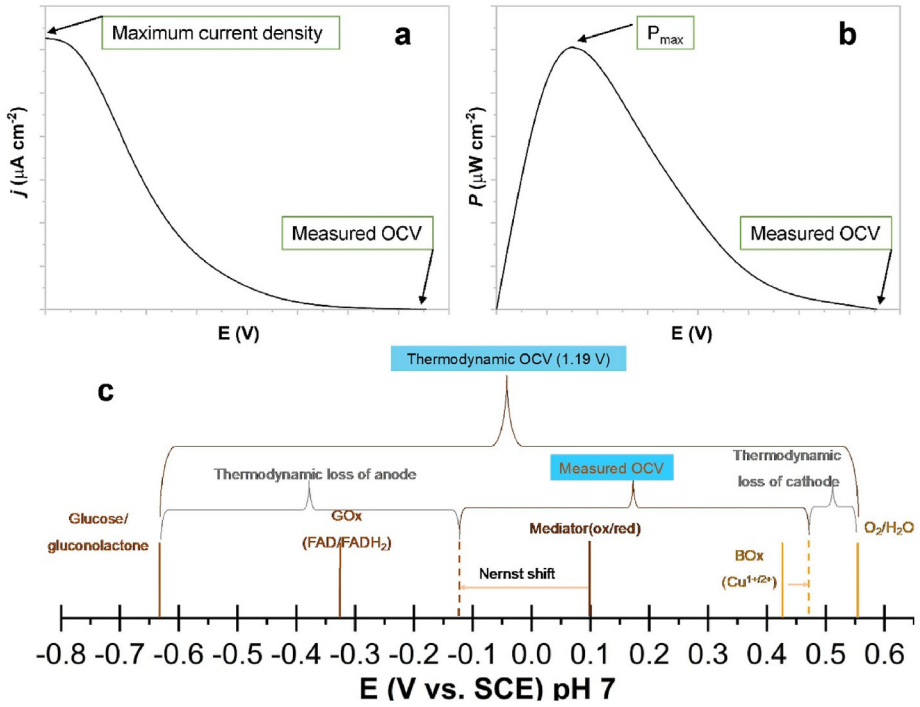

Fig. 4. Typical polarization curve (a) and power density profile (b) of an EBFC. (c) Potential spectrum for the reaction of a glucose/O_2 EBFC consisting of a GOx bioanode with a mediator, undergoing two-electron oxidation under standard conditions, and a BOx-based biocathode undergoing DET.

OCV is the largest output potential that a single EBFC can generate, which in practice is generally less than 1 V [2]. The measured OCV is typically lower than the thermodynamic value (1.19 V for a glucose/O_2 EBFC undergoing two-electron glucose oxidation under standard conditions), due to thermodynamic losses, namely, overpotentials at the anode and cathode (Fig. 4c). In practice, the polarization curve of the individual bioelectrode in a three-electrode system is required to determine the limiting electrode of an EBFC. The measured OCV is consistent with the difference between the onset potential of the anode and cathode [20,46]. The onset potential of a mediated GOx bioanode is typically determined by the redox potential of the mediator being employed. Due to the Nernst shift, the measured onset potential of the bioanode is generally lower than the redox potential of the mediator. Similarly, the onset potential of a DET-based BOx biocathode will be slightly higher than that of the Cu center, but still lower than that of the formal potential of oxygen reduction. It can be seen from Fig. 4c that the overpotential at the anode is the major limiting factor of a GOx/BOx-based glucose/O_2 EBFC, which could be improved by using a redox mediator with a redox potential close to but still higher than that of flavin [47].

In the literature, P_{max} in terms of geometric surface area for EBFCs is in the range of 0.1–1000 μW cm^{-2}, exceeding 1 mW cm^{-2} in a few instances [2]. Given the rapid development of low-energy-consumption bioelectronics, improving output potential should be a much higher priority than P_{max} in future work to make EBFCs feasible for application.

Operational stability is another important parameter. It cannot be determined from the power density profile but can be investigated by measuring power over the course of time. Due to the fragile nature of enzymes and the absence of the renewal processes present in living cells, the lifespan of an EBFC is generally a matter of days, making this another limiting factor for practical applications.

3. Self-powered biosensing

In the context of bioelectrochemistry, both EBFCs and amperometric biosensors rely on the construction of enzyme-modified electrodes, because the employed enzyme can be both catalytically active and selective. For example, blood glucose can be the fuel of an EBFC and also the analyte of a biosensor, which is of great significance for diabetics. Unsurprisingly, Katz and Willner in 2001 proposed the concept of "self-powered" biosensors, using the cell voltage of an EBFC as a sensitive signal correlated to the fuel concentration [48]. This type of sensing device operates without an external power supply, opening up new opportunities for instrument-free biosensing. During the past two decades, this field has expanded greatly from detecting fuels to sensing enzyme inhibitors, antigens, and cancer cells [18,22,49–51]. Instead of presenting an exhaustive rundown of the literature, the author has critically selected and summarized representative reports, categorizing the various self-powered biosensors based on their working mechanisms.

The first major group relies on the correlation between the power/voltage output of an EBFC and the biofuel concentration. Various analytes, including glucose, fructose, lactate, ethanol, and cholesterol, have been detected with this approach by constructing the corresponding EBFCs [49]. To achieve this goal, the power output of an EBFC should be limited by the bioanode. In other words, the limiting current density of a biocathode should be much higher than that of the bioanode in the presence of various fuel concentrations. If a typical oxygen-reducing biocathode is used, the local oxygen concentration should remain at a level that guarantees the biocathode generates a higher limiting current density than the bioanode. It is always a challenge to achieve implantable self-powered biosensing using an oxygen-reducing biocathode, due to the low oxygen level in vivo [5].

Another obstacle is to develop a truly "instrument-free" or "expensive-instrument-free" device, as the majority of the reports still require a potentiostat to measure the voltage/current. An innovative solution is to use electrochromic materials such as Prussian blue to function as a consuming cathode with an enzymatic bioanode [52–55]. Such a device leads to a simple and distinct visual display of analyte concentration readable with the naked eye. A quantitative self-powered electrochromic biosensor was demonstrated by Aller Pellitero et al. [54] by horizontally coupling a GOx-based bioanode to a Prussian blue-based cathode (Fig. 5). Prussian blue is reduced to colorless Prussian white by accepting electrons transported externally from the bioanode. The dimensional design here controls the current path, enabling the Prussian blue to fade from the region close to the anode due to the minimal electric resistance. The

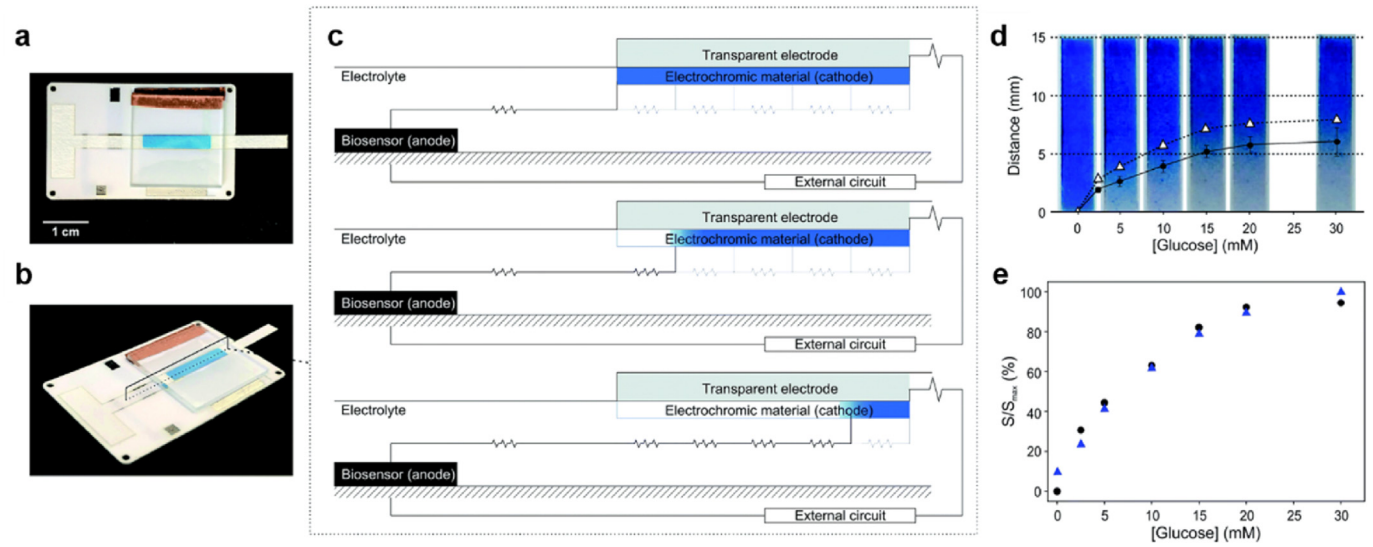

Fig. 5. (a, b) Digital photographs of a self-powered biosensing device. (c) Schematic drawing of the device from the side, showing a GOx-based bioanode placed to the left of a Prussian blue cathode. (d) Digital photos of the Prussian blue display, overlaid with different glucose concentrations. (e) Calibration curve of the normalized maximum biosensor current (blue triangles) and color edge position (black circles) versus glucose concentration. Reprinted from Ref. [54] with permission.

gradual color change along the electrode length is dependent on the analyte concentration or reaction time (Fig. 5c), resulting in a correlation between the edge of the color and the glucose concentration over time (Fig. 5e). An organic electrochromic timer has also been constructed in a similar cell configuration [56].

The major challenge for electrochromic biosensors is their relatively low precision, which could be improved with optimized device design and the assistance of widely available smartphones to enable quantitative readouts. Another innovation is the illumination of light emitting diodes (LEDs) using EBFCs, achieved by charging an external capacitor via a charge pump circuit until the capacitor reaches its maximum capacity [57]. The frequency of the light emitted from the LED reflects the fuel/analyte concentration. The present challenge for this route is to obtain LED illumination with visible light, which requires a rather high input voltage [58].

The second group of self-powered biosensors is based on the linear change in power/voltage output due to inhibition/biorecognition events from analytes. (i) Enzyme inhibitors, such as the sensor's own catalytic product [59], heavy metals [60], and toxic compounds [61], can reversibly or irreversibly inhibit enzymatic activity, thus leading to a relational power/voltage output decrease along with decreasing inhibitor concentration. The major challenge for this type of sensor is selectivity, as the presence of many species co-existing in a complex sample could lead to a drop in EBFC performance. A Cu^{2+}-inhibited GOx-based bioanode can be reactivated by ethylenediaminetetraacetic acid (EDTA) due to chelation to Cu^{2+}, in turn leading to a correlation between the EDTA concentration and power output [62]. (ii) Additional biorecognition elements, e.g., antibodies, DNA strands, and aptamers, in contact with the bioelectrode can give EBFCs sensing ability towards non-substrates. This approach greatly expands the scope of analytes. The specific biorecognition, due to antigen–antibody interaction, DNA–DNA hybridization, and aptamer interactions with analytes (i.e., antibodies [63], DNA [64], proteins, antibiotics, and cancer cells [65]), induces competition, steric hindrance, or electrostatic repulsion. This affects the mass transport of the enzyme substrate or diffusing mediator, causing decreased power/voltage output. In an ultrasensitive self-powered

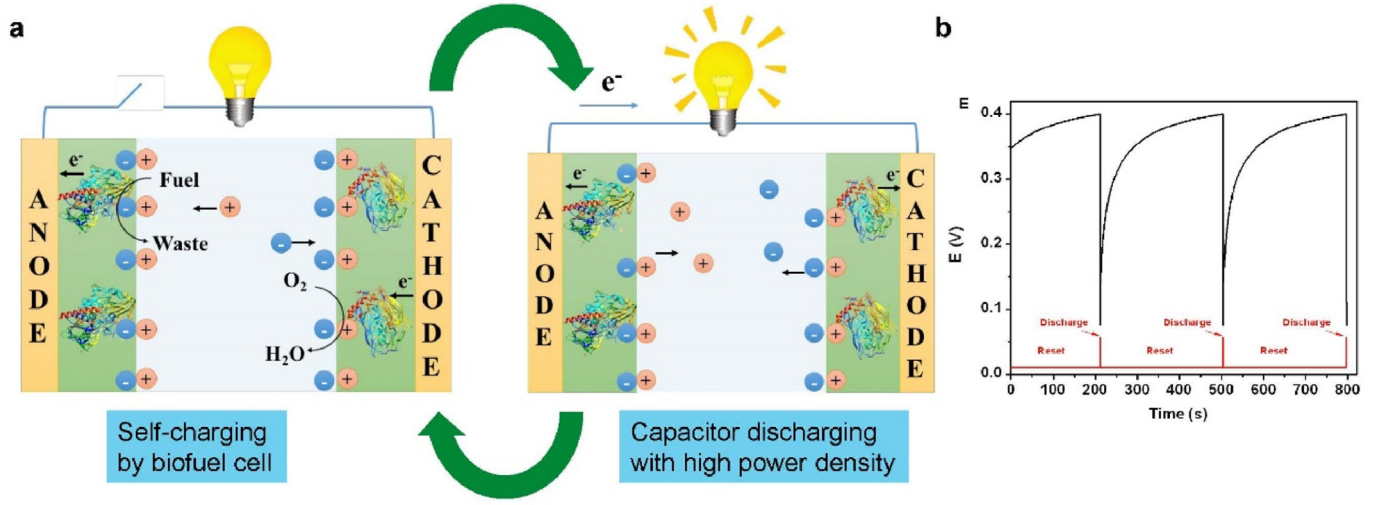

Fig. 6. (a) Schematic drawing of a self-powered biosupercapacitor working in a sequence of self-charging (left) and galvanostatic discharging (right). (b) Three cycles of the typical charge/discharge profile of the hybrid device (black line) and the experimental setup of the repeated sequence of reset and discharging for 0.5 s (red line). The curve in black shows the measured potential signal. Reprinted from Ref. [19] with permission.

cytosensor to detect acute leukemia CCRF-CEM cells [51], Gai et al. immobilized an aptamer on the cathode; this was regenerated by a moderate temperature change to reversibly disrupt the aptamer–cell interaction, exhibiting considerable reusability. In another configuration employing a sandwich immunoassay, the glucose-oxidizing enzyme was conjugated to a signal antibody, which was attached to an anode coated with a captured antibody in the presence of the analyte: carcinoembryonic antigen (CEA) [63]. Thus, the power output of the proposed glucose/O_2 EBFC showed increased dependence on the CEA concentration. This sensing platform was also combined with a microfluidic paper-based analytical device, enabling low-cost applications [63]. However, combining EBFCs with biorecognition elements obviously greatly increases the complexity of the bioelectrode's construction.

4. Self-powered pulse generator

A pulse generator is an important unit found in pacemakers, neurostimulators, defibrillators, and distal stimulators, delivering repeatable electrical pulses to stimulate the nervous system. A pacemaker can generate pulses in the potential range of 0.5–1.5 V and a width of ca. 0.5 ms to pace the heart [66]. In 2017, the author and associates first demonstrated the possibility of a self-powered pulse generator based on a glucose/O_2 EBFC (Fig. 6) [19]. In this case, instead of using the EBFC as the power unit to activate an external pulse generator, the EBFC is utilized directly as the pulse generator permitting the output pulses. This is a hybrid device of a supercapacitor and EBFC. An osmium complex modified redox polymer and poly(3,4-ethylenedioxythiophene) (PEDOT) composite layer is electrochemically deposited onto NPG to immobilize glucose dehydrogenase (GDH) and BOx for the bioanode and biocathode, respectively. Os redox polymer serves as the ET mediator, while PEDOT contributes to the pseudocapacitance of the bioelectrode. The assembled self-powered supercapacitor can function in a self-charge and discharge sequence (Fig. 6b): (i) Under resting conditions, the internal capacitor is electrostatically charged by the thermodynamically induced potential difference built between the biocathode and bioanode due to the bioelectrochemical reactions, driving the voltage profile close to the OCV of the EBFC (Fig. 6a). (ii) The power stored in the biosupercapacitor can be subsequently discharged at high current densities in a short period, leading to high-power-density pulses (Fig. 6b). Notably, the EBFC alone only generates a maximum current density of 28.9 μA cm^{-2}, while the hybrid device discharges pulses at 2 mA cm^{-2}. Connecting three cells in series can deliver 0.2 Hz pulses (10 μA, 0.5 ms) with a stable output potential of 0.7 V for 20,000 cycles.

The concept of a self-powered biosupercapacitor, i.e., the coupling of an EBFC and a supercapacitor, dates back to 2014, when Cosnier's [67] and Shleev's [68] research groups separately proposed such an approach to achieve high-power-density output from an EBFC. Before that, the high electrochemical capacitance current densities induced by nanomaterial modifiers for enzyme immobilization were generally ignored. The emergence of a self-powered biosupercapacitor led the research community to utilize the electrochemical capacitance of the bioelectrode, either from electrochemical double-layer capacitance due to high-surface-area nanomaterials [69] or from pseudocapacitance due to a conducting polymer and a redox active polymer [70–72]. Self-powered supercapacitors provide the possibility of healing of chronic wounds by delivering electrical pulse stimulation, although this has not yet been fully explored. The device also holds the promise of reflecting fuel concentration based on charging speed or discharging frequency. It should be noted that the voltage of the generated pulse, which may not be satisfactory for medical applications requiring extremely high voltage, is still limited by the measured OCV of an EBFC.

In the context of wearable EBFCs, perspiring human subjects provide the fuel [9,58]. To remove the need for sweat, a quasi-solid-state and flexible self-powered supercapacitor using a poly(vinyl alcohol) hydrogel electrolyte with preloaded sugar fuel was developed [20], able to generate power when the human subject is in a resting state. The flexible device can deliver pulses for at least 600 cycles, with a power density over 10-fold higher than that from the EBFC alone. A report on the miniaturization of a biosupercapacitor, which occupies only 1 nL, indicates exciting progress in work on micropower sources [73]. A micro/nano-sized self-powered biosupercapacitor thus can be achieved in the future.

5. Self-powered therapeutic system

The direct use of EBFCs as a therapeutic tool is possible. External electrical stimulation can be utilized to promote the biological processes of wound healing that involves cell migration and proliferation. Kai et al. used animals tests to prove that the generation of an ionic current by a fructose/O_2 EBFC on a stretchable hydrogel fixed onto skin can be useful for the treatment of skin wounds [74]. To improve the efficiency of iontophoresis, ion-conductive porous microneedles have been further coupled with an EBFC [75]. Park et al. found that the electrostimulation generated by a single glucose/O_2 EBFC could be a promising way to enhance the functionality of human embryonic stem cell-derived cardiomyocytes [76]. In another study, human dermal fibroblast cellular motility, a key biological factor in tissue and organ wound healing after device implantation, can be significantly enhanced by a single glucose/O_2 EBFC [77], which employs GDH rather than GOx (the latter generates H_2O_2 as a by-product, causing cytotoxicity).

Therapy can also be achieved by using EBFCs directly to release drugs. In 2012, Katz's group proposed a self-powered "sense–act–treat" system relying on an EBFC, consisting of a lactate-oxidizing bioanode and a cathode comprised of a PEDOT layer with doped anionic acetaminophen [78]. The presence of lactate can initiate the release of acetaminophen, due to the reduction/de-doping of the PEDOT layer. However, the enzymes are not immobilized in this case, so the system is not suitable for implantable applications. Katz's group developed Fe^{3+} cross-linked alginate polymer containing large biomolecules as the cathode [79–81], then used this to release biomolecules upon receiving electrons from the enzymatic bioanode. The limitations of this system are that the additional release of Fe^{2+} may be unwanted, and the alginate polymer suffers from physical instability in high pH. Local pH change induced by enzymatic catalytic reactions has also been used as a strategy to release model drugs from EBFCs [82,83], widening the scope for therapeutic application.

An elegant design for transdermal drug release was reported by Ogawa et al. [84], who developed an iontophoresis patch (Figs. 7a and b). It is a fully enzymatic fructose/O_2 EBFC operating on a UV-cured hydrogel electrolyte containing the drug molecules and the fructose fuel. The patch can be mounted on the skin and generates a transdermal ionic current with osmotic flow from the bioanode to the biocathode, administering the release of ascorbyl glucoside and rhodamine B from the hydrogel into the skin.

A compact, implantable, and switchable EBFC-enabled self-powered drug-delivery system has been developed (Fig. 7c) [85], introducing an additional conductive polymer/drug layer on a Os redox polymer/BOx biocathode. When coupled with a GOx-based bioanode, the resultant glucose/O_2 EBFC can rapidly release model drugs that are incorporated into the conductive polymer layer. In addition to anionic species, cationic compounds can also be released, through the careful design of the additional doped conductive polymer layer. This approach enables controllable drug release—i.e., the device is switched "on" when the EBFC is discharging and "off" when the EBFC is held at open circuit. Antibiotic ampicillin can also be released via such a system [86], offering the potential to make the surfaces of medical implant devices antimicrobial and to promote wound healing.

Another noteworthy example of a self-powered "diagnosis–therapy–evaluation" platform is a non-enzymatic glucose/O_2 fuel cell utilizing robust abiotic catalysts, developed by Wang et al. [21]. The anode is additionally modified with hollow mesoporous silica loaded with the drug doxorubicin via a partial complementary DNA double strand, while

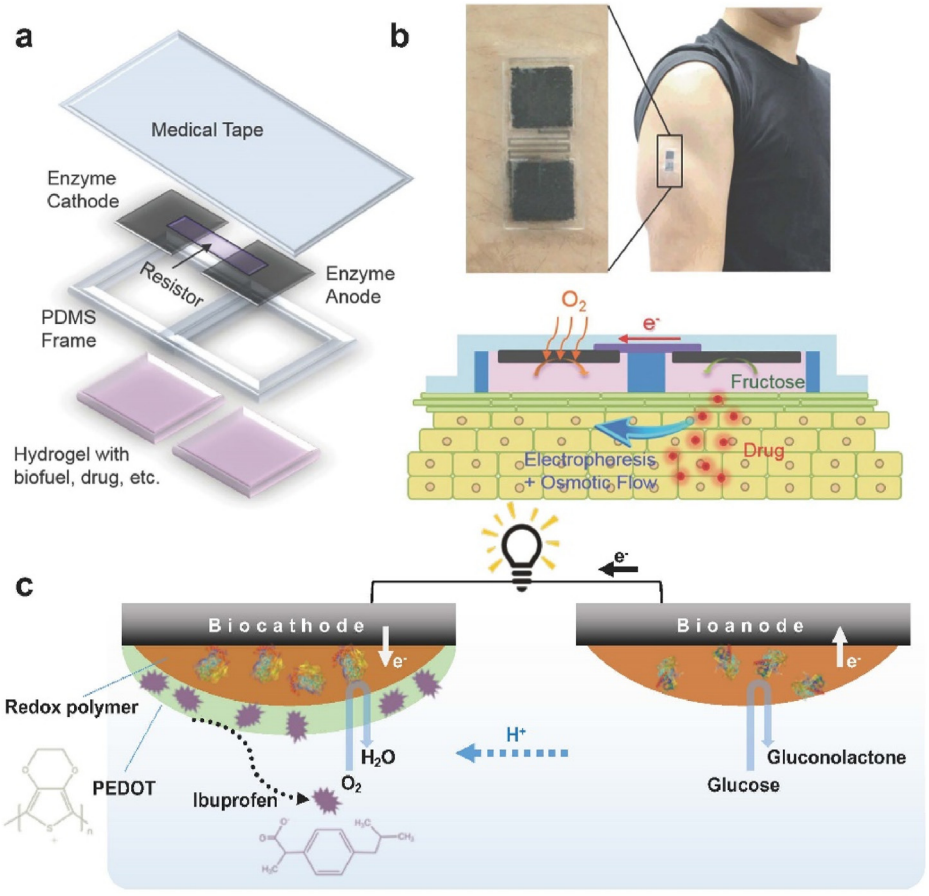

Fig. 7. (a) Schematic drawing of the assembly of a transdermal iontophoresis patch based on a fructose/O_2 EBFC. (b) Digital photo of the patch mounted on a human arm, and a schematic of the drug-delivery mechanism. Reprinted with permission from Ref. [84]. (c) Schematic illustration of a compact EBFC-enabled self-powered drug-delivery system with an additional PEDOT/ibuprofen layer on the biocathode [85].

Table 1
Key features of representative EBFC-enabled self-powered bioelectronics.

Bioelectronics	EBFC structure	EBFC parameter	Remarks	Ref.
Self-powered biosensing	Anode: GOx or LDH; cathode: *Cyt c*/COx[a]	OCV: n/a P_{max}: n/a	EBFC output voltage is correlated to the concentration of glucose/lactate, in a range of 1–80 mM; it requires a potentiostat.	[48]
	Anode: GOx; cathode: Prussian blue (consuming type)	OCV: < 0.5 V; P_{max}: 13 μW cm^{-2} (30 mM glucose)	Glucose concentration is coulometer readable; potentiostat-free.	[54]
Self-powered biosupercapacitor	Glucose/O_2 EBFC; anode: GOx; cathode: laccase	OCV: 1 ± 0.1 V P_{max}: 16 mW	The high electrochemical capacitance of CNTs is used.	[67]
	Glucose/O_2 EBFC; anode: CDH; cathode: BOx	OCV: 0.56 V; P_{max}: 7 μW cm^{-2}	It can generate a power of 1.2 mW cm^{-2}, 170 times higher than the EBFC alone.	[68]
Self-powered pulse generator	Glucose/O_2 EBFC; anode: FAD-GDH; cathode: BOx	OCV: 0.46 V; P_{max}: 1.3 μW cm^{-2}	It can deliver pulses of 10 μA for 0.5 ms at a frequency of 0.2 Hz; the potential of the pulse is still limited by the OCV.	[19]
Self-powered drug release	Anode: LDH; cathode: PEDOT-acetaminophen (consuming type)	OCV: 0.4 V; P_{max}: 33.8 μW cm^{-2}	A self-powered "sense–act–treat" system; however, enzymes are not immobilized.	[78]
	Fructose/O_2 EBFC; anode: FDH; cathode: BOx	OCV: 0.75 V; P_{max}: ca. 60 μW cm^{-2}	Iontophoretic delivery of ascorbyl glucoside.	[84]
	Glucose/O_2 EBFC; anode: GOx cathode: BOx with drug-doped conductive polymer	OCV: ca. 0.4 V; P_{max}: ca. 1 μW cm^{-2}	Anionic and cationic molecules can be released upon rational design of conductive polymer; switchable and controllable.	[85]
Self-powered "diagnosis–therapy–evaluation"	Anode: modified porous gold nanobowl; cathode: hollow mesoporous N-doped carbon sphere	OCV: ca. 0.59 V; P_{max}: 145 ± 1.2 μW cm^{-2}	A non-enzymatic glucose/O_2 fuel cell utilizing robust abiotic catalysts; a combination of self-powered biosensing and drug release.	[21]

Note [a]: *Cyt c*/COx: cytochrome *c*/cytochrome oxidase; LDH: lactate dehydrogenase; CDH: cellobiose dehydrogenase.

the cathode is further modified with a peptide that can bind to doxorubicin-induced apoptotic cancer cells. A tumor biomarker can competitively hybridize with the partial complementary DNA, leading to the release of the drug carriers. Alleviation of the blocking effect from the drug carriers on the anode is reflected by increased power output from the fuel cell, signaling a cancer risk. The released doxorubicin causes cell apoptosis, which can be captured on the cathode. This also leads to a blocking effect upon the oxygen supply, and thus decreased power output

from the fuel cell. This process serves to evaluate the therapeutic effect of doxorubicin. The electrode configuration here is sophisticated, but the switch from anode dependence to cathode dependence has not been well demonstrated.

6. Conclusion and perspectives

Activation of state-of-the-art bioelectronics by a single EBFC is constrained by voltage mismatch. Self-powered devices using EBFCs directly to achieve certain functions represent a promising solution. This contribution has summarized the direct use of EBFCs for self-powered biosensing, pulse generation, and therapy. The key features of the representative EBFC-enabled self-powered bioelectronics discussed here are summarized in Table 1. Overall, EBFC-enabled self-powered biosensing is highly selective and is approaching the point of being "instrument-free" or "expensive-instrument-free". Autonomous pulse generation may be more efficient over continuous low-power-density electrostimulation; this requires further validation. Additional complexation of the bioelectrode can lead to new functionality, especially controllable drug release. An autonomous "sensing-and-actuating" approach is promising, allowing both sensing and on-demand drug release.

In addition to above aspects, the scope for using EBFC-based bioelectronics could be further expanded. For example, the EBFC has been revealed as a novel self-powered time–temperature integrator [87], which could be applied as a smart label in food quality monitoring and the cold chain. A very recent innovation of EBFC-enabled artificial muscles [88] is a great example of interdisciplinary efforts, bringing EBFCs into the field of soft microrobots, biodegradable devices, and implantable artificial muscles. Electro-osmosis led by an EBFC, which may be used in numerous medical applications in the future, has been utilized to avoid the "dry-eye" side effect of a contact lens by maintaining tears between the lens and the ocular surface [89].

Despite the intriguing properties of EBFC-based bioelectronics, the intrinsic challenges of EBFCs, such as limited power density and lifetime, have not yet been solved. Such limitations could further hinder the practical application of these bioelectronics. Fundamental studies to tackle these intrinsic challenges are still needed. Another important factor requiring further investigation is the biocompatibility of EBFCs for medical applications.

Conflict of interest

The author declares there to be no conflict of interest.

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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