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Review

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Self-Powered Biosensors

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ABSTRACT: Self-powered electrochemical biosensors utilize biofuel cells as a simultaneous power source and biosensor, which simplifies the biosensor system, because it no longer requires a potentiostat, power for the potentiostat, and/or power for the signaling device. This review article is focused on detailing the advances in the field of self-powered biosensors and discussing their advantages and limitations compared to other types of electrochemical biosensors. The review will discuss self-powered biosensors formed from enzymatic biofuel cells, organelle-based biofuel cells, and microbial fuel cells. It also discusses the different mechanisms of sensing, including utilizing the analyte being the substrate/fuel for the biocatalyst, the analyte binding the biocatalyst to the electrode surface, the analyte being an inhibitor of the biocatalyst, the analyte resulting in the blocking of the bioelectrocatalytic response, the analyte reactivating the biocatalyst, Boolean logic gates, and combining affinity-based biorecognition elements with bioelectrocatalytic power generation. The final section of this review details areas of future investigation that are needed in the field, as well as problems that still need to be addressed by the field.

KEYWORDS: *biosensors, biofuel cells, enzymatic fuel cells, inhibition, reactivation, logic gates*

Most scientists are familiar with the field of biosensors due to the commercial acceptance of the glucose biosensor for testing the blood glucose level in diabetic patients. Biosensors are typically defined as a transducer covered with a chemically selective layer that contains a biological entity. That biological entity could be a protein (enzyme or antibody), a nucleic acid (single stranded DNA or a deoxyribozyme or an aptamer), an organelle (mitochondria or thylakoid membranes of plant cells), or even a living organism (microbe) or tissue. The transducer could be measuring photons, electrons, or another physical property (i.e., temperature changes). One of the most common transducers is the electrode. Electrochemical biosensors are most commonly amperometric biosensors, where a constant potential is applied to the sensing electrode versus a reference electrode and the current between the sensing electrode and counter electrode is measured.[1,2] This current is then related to the concentration of the analyte being detected.

This type of biosensor is very common, because of the simplicity of the electronics required and the high sensitivity of this method. Other techniques include voltammetric,[3] impedimetric,[4] and galvanostatic electrochemical methods, but amperometry and these other electrochemical techniques all require a potentiostat/galvanostat to operate and that potentiostat/galvanostat requires power, as does the signal processing and the signaling device (i.e., electronic display, buzzer, Bluetooth communication to a cell-phone, etc.). Therefore, in 2001, Willner and Katz coined the term "self-powered biosensor" for a biofuel cell that generated power that was proportional to the concentration of the analyte.[5] This was the dawn of a new type of electrochemical biosensor, but also the merging of two fields: the fuel cell field and the sensor field. The sensor field is primarily made up of electroanalytical chemists who typically operate in 3-electrode mode with a focus on improving sensitivity and selectivity via materials strategies, and the fuel cell field mainly operates in 2-electrode mode (anode and cathode) and the focus is to generate a large open circuit potential, large short circuit currents, and maximum power densities via improvements in catalysts, materials, interfaces, and cell designs. Therefore, early in the review, we will have a section focused on the issues that address selectivity, potential, and power from those differing points of view.

First, this review will provide some background on the properties and types of electrochemical cells that are utilized in self-powered biosensors. In order for an electrochemical biosensor to be self-powered, the sensing electrode must be combined with a second electrode to yield a galvanic cell. This could be a traditional metal-based battery or fuel cell. For instance, Crooks and co-workers developed a self-powered trypsin biosensor that is a Mg/Fe^{3+} battery that is not functional until the presence of trypsin breaks down a protein layer and an Al protection layer that completes the circuit and makes a self-powered biosensor.[6] This concept was further expanded by Zhong Lin Wang's group to make a hybrid device with a Cu|Al galvanic cell and triboelectric nanogenerator for

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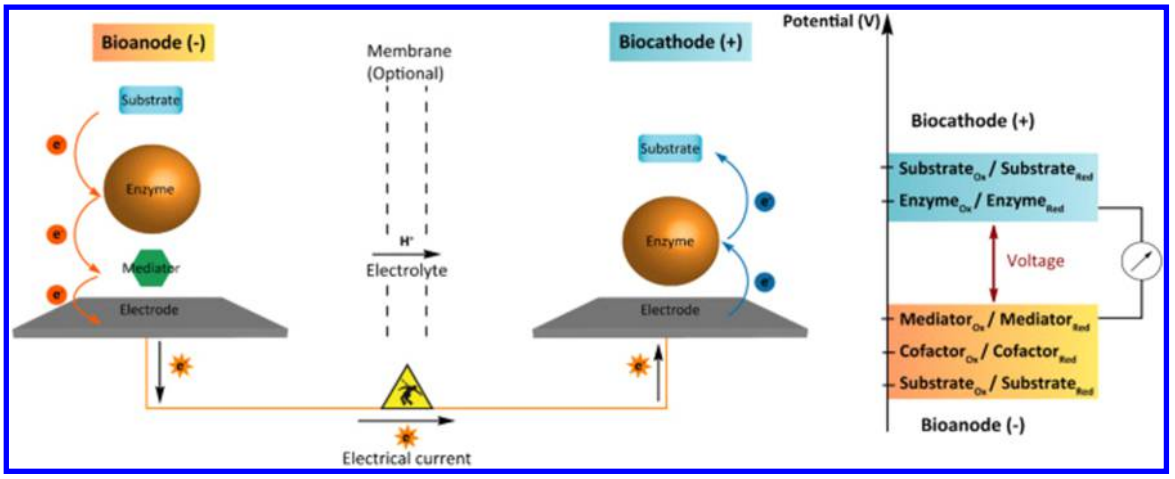

Figure 1. Schematic of an enzymatic biofuel cell utilizing a mediated bioanode and a direct electron transfer-based biocathode. Reprinted with permission from Rasmussen, M.; Abdellaoui, S.; Minteer, S. D. Enzymatic biofuel cells: 30 years of critical advancements. *Biosens. Bioelectron.* **2016**, *76*, 91−102.[16] Copyright 2016 Elsevier.

increased voltages for powering signaling devices.[7] This combination system utilized a Pt electrode for hydrogen peroxide detection, but could be easily expanded to a biological selective layer (i.e., enzymes, antibodies, etc.). Although there are examples of traditional battery systems being employed, most electrochemical galvanic cells utilized in self-powered biosensors are biofuel cells, where the catalyst at the anode and/or the cathode is of biological origin. The historical biofuel cell utilized in self-powered biosensors was an enzymatic fuel cell utilizing an oxidoreductase enzyme or enzymes to catalyze the oxidation of fuel at the anode and/or the reduction of oxygen or peroxide at the cathode,[8] as shown in Figure 1. Organelle-based redox catalysts including thylakoid membranes and mitochondria have also been employed more recently.[9,10] Most promising has been the recent work utilizing microbial fuel cells with microbial biofilms at the anode (and occasionally the cathode) as the electrocatalysts.[11−14] Finally, deoxyribozyme-based catalysts have been used in combination with enzymatic catalysts to form hybrid biofuel cells that can be utilized for self-powered biosensors.[15]

Biofuel cells are typically classified by their mode of bioelectrocatalysis as either direct electron transfer or mediated electron transfer, depending on whether electrons can transfer directly from the bioelectrocatalyst to the electrode or not, as described in many recent reviews.[16−19] Figure 1 shows an enzymatic biofuel cell where the bioanode is in mediated electron transfer configuration (a mediator shuttles electrons from the enzyme to the anode), while the cathode is in direct electron transfer configuration (electrons are transferred directly from the electrode to the enzyme). Most self-powered biosensors using enzymatic fuel cells typically utilize a redox mediator (small molecule or redox polymer) to shuttle the electrons between the enzyme and the electrode. Most microbial fuel cells utilize direct electron transfer, where microbial biofilms have internal mechanisms for shuttling electrons between the inside of the cell and the electrode surfaces. However, there are examples utilizing mediators like phenazines to shuttle electrons in microbial fuel cells and examples of direct electron transfer systems in enzymatic fuel cells. As will be shown in future sections, the mode of electron transfer affects the materials strategies for improving the analytical performance of the biosensor.

It is important to note that although the sensor is typically the biofuel cell, the biofuel cell can be used to power the sensor, as separate devices. For instance, Atanassov et al. combined a biosensor with a biofuel cell on a patch for detecting lactate in sweat.[20] This strategy allows you to use a high concentration compound (i.e., glucose in the bloodstream) as a fuel for the biofuel cell, but use that power to measure a much lower concentration analyte at the sensing electrode. It is important to note that this type of system will require potentiostat circuitry, so it has advantages and disadvantages.

SELECTIVITY

Selectivity in biosensors usually comes from the biological entity in the chemically selective layer. From a simple perspective, enzymes, deoxyribozymes, organelles, and living cells selectively catalyze a reaction with the analyte and antibodies and aptamers selectively bind the analyte. However, that is not the only mechanism for selectivity in a biosensor. Recent research has explored enzyme inhibition, reactivation, and the use of logic gates to allow for the measurement of lower concentrations of analytes and to allow for the determination of nonredox active analytes. This will be detailed in specific examples in the next sections. It is also important to note that all biological entities and mechanisms do not have the same level of selectivity. For instance, individual isolated and purified enzymes are far more selective to their substrate than an organelle or a microbe, which typically have broad substrate specificity. Typically, antibodies bind with a higher affinity to their analyte than aptamers, and although enzymes might be very specific for their substrate, they are often inhibited by large classes of molecules. All of these issues need to considered when designing a self-powered biosensor.

IMPROVING THE PERFORMANCE OF A GALVANIC ELECTROCHEMICAL CELL—VOLTAGE VERSUS POWER

Generally, researchers would think a "self-powered" sensor design would focus on power, but in order to power a signaling device, the operating potential must be positive and relatively large. Most electronic devices, even with power management, require a potential greater than 0.4 V for operation. The standard reduction potentials of every anodic and cathodic

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redox reaction can be used to predict a theoretical open circuit potential. However, potentials of biofuel cells are typically significantly lower. The potential is not driven by the reaction being catalyzed by the oxidoreductase enzyme, but by the cofactor redox potential that is transferring the electrons to the electrode. This is true for direct electron transfer, but when mediators are used to shuttle electrons from that cofactor to the electrode, then open circuit potentials are further decreased by the potential difference between the cofactor and the mediator, as shown in Figure 1. Therefore, it is critically important to choose mediators with standard reduction potentials that are quite close to the standard reduction potentials of the cofactors. This is rarely a concern with amperometric biosensors, but is a large concern for self-powered biosensors. However, recently, there are examples of voltage boosters used to increase voltage, when potentials are less than 0.4 V, so this problem is becoming less of an issue.[21]

Since the other main issue is power output, there is a goal of producing a large current density at large operating potential since power is equal to the product of voltage and current. The goal of high power can be obtained by combining good mediator selection as discussed above with materials design strategies to improve the current density. These strategies include the use of high surface area, nanostructured, or hierarchical structured materials. Most frequently those materials are carbon-based conductive materials. Carbon nanotubes are probably the most frequently used nanomaterial in biofuel cells and self-powered biosensors, although graphene and other carbon fibers have also been popular.[22−25] However, it is important to point out that recent research has also combined enzymatic biofuel cells with capacitors[26,27] or used the enzymatic biofuel cells as a biosupercapacitor[28−31] itself to circumvent current densities that are too small for the signaling electronics.

■ ENZYMATIC SELF-POWERED BIOSENSORS

The first self-powered enzymatic biosensors were, not surprisingly, focused on glucose. Willner and Katz developed a mediated glucose biofuel cell and utilized it for sensing glucose.[5] In this case, the analyte glucose is being oxidized by an oxidoreductase enzyme at the anode while oxygen is being consumed by cytochrome c oxidase at the cathode. This design has been expanded to other enzymes (glucose oxidase versus glucose dehydrogenase, laccase versus bilirubin oxidase), but the theory is the glucose analyte is being consumed as the fuel for the fuel cell.[32−36] This concept has been expanded to other analytes, including fructose,[37] lactate,[20,21,33,38,39] acetylcholine,[40] ethanol,[41] oxygen,[42] ascorbic acid,[43] and cholesterol.[44] The cholesterol self-powered biosensor is particularly interesting, because it only uses a single enzyme (cholesterol oxidase). As shown in Figure 2, cholesterol oxidase oxidizes cholesterol for mediated bioelectrocatalysis at the anode and produces peroxide for Prussian blue electrocatalysis at the cathode. In these cases, current scales with concentration of analyte below the enzyme K_m, which means that low concentrations of analytes result in low power, which limits the application of these sensors to higher concentration applications (i.e., micromolar to millimolar concentration analytes).

There has also been a slight modification to this strategy to include affinity-based biorecognition elements. For instance, Guo et al. designed a self-powered immunosensor where the cathode enzyme (bilirubin oxidase) of the glucose/oxygen enzymatic biofuel cell is not immobilized on the cathode, but

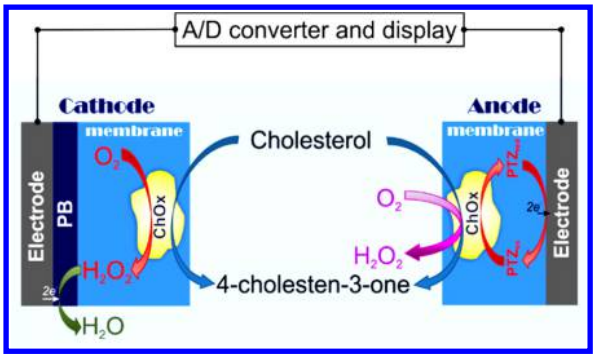

Figure 2. Schematic of a self-powered cholesterol biosensor, where PB is Prussian blue, ChOx is cholesterol oxidase, and PTZ is a phenathiazine. Reprinted in part with permission from Sekretaryova, A. N.; Beni, V.; Eriksson, M.; Karyakin, A. A.; Turner, A. P.; Vagin, M. Y., Cholesterol self-powered biosensor. *Anal. Chem.* **2014**, *86*, 9540−9547.[44]

rather is attached with an antibody to a carbon nanotube.[45] The analyte is passed over a cathode modified with a secondary antibody for the analyte allowing the analyte to bind followed by the carbon nanotube. When the analyte is present, this sandwich assay binds the bilirubin oxidase to the cathode allowing for enzymatic bioelectrocatalytic power generation. This same concept has been used for self-powered DNA sensors, where hybridization is used to immobilize the enzyme at either the anode or the cathode of the enzymatic biofuel cell. For instance, Yu et al. developed a DNA sensor where the cathode was a platinum electrode catalyzing oxygen reduction and the anode was modified with a small single strand of DNA that hybridized with the analyte followed by hybridization of the rest of the analyte DNA with a different single strand of DNA that contained glucose oxidase and horseradish peroxide which oxidized glucose.[46] This resulted in a detection limit of 6.3 fM.[46] This shows the added benefit of using the affinity-based biorecognition elements with the enzyme biocatalysts.

After the use of analyte as fuel, inhibition-based enzymatic self-powered biosensors became popular. Enzymes can be inhibited reversibly or irreversibly by a variety of different compounds that may or may not be electrochemically active. For instance, alcohol dehydrogenase is competitively inhibited by its product acetaldehyde and, therefore, researchers have designed a self-powered acetaldehyde biosensor utilizing an ethanol enzymatic biofuel cell.[47] A similar approach has been used for mercury,[48] cyanide,[49] perfluorooctane,[50] and arsenic sensing.[51] Types of inhibition can be competitive, non-competitive, uncompetitive, and mixed inhibition. If inhibitors are irreversible, then the sensor will not be reusable, but since most inhibitors are reversible inhibitors, then the self-powered sensors can be reused or part of online or in-line sensing systems. The challenge with inhibition-based biosensors is they are turn-off self-powered biosensors not turn-on (i.e., the power goes away in the presence of the analyte rather than being generated in the presence of the analyte), as shown in the top half of Scheme 1.

Similar to inhibition mechanism, blocking effects have also been studied for nonsubstrate based sensing. In this system, an affinity-based biorecognition element is added to the electrode (i.e., antibody, aptamer, DNA) and when the biorecognition element binds the analyte, it blocks the transport of substrate to the enzyme or enzyme to the electrode resulting in a turn-off biosensor. Unlike inhibition-based sensors that frequently have

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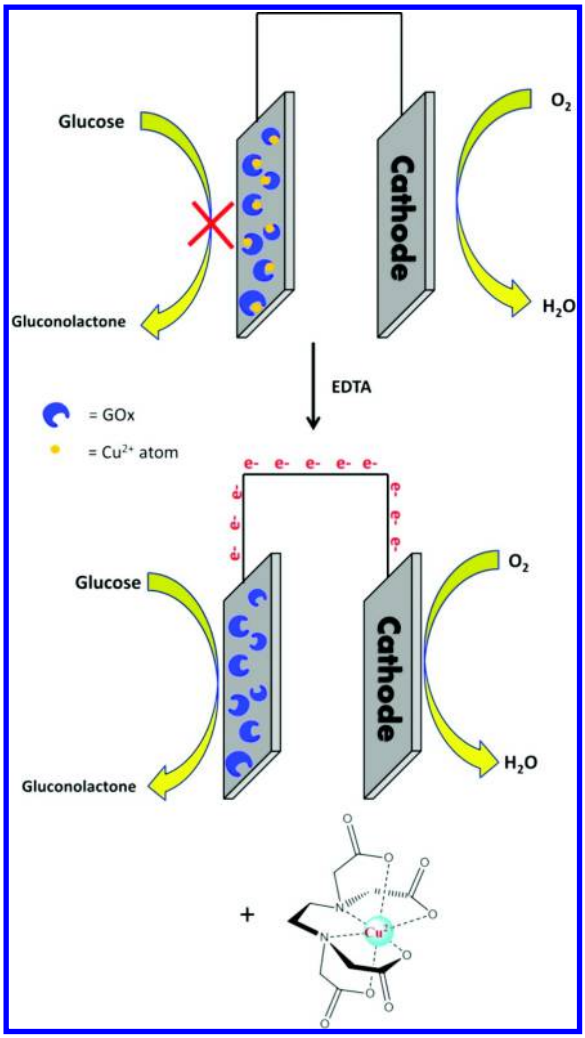
Scheme 1. EDTA Reactivation of a Cu^{+2} Inhibited Glucose Biofuel Cell[a]

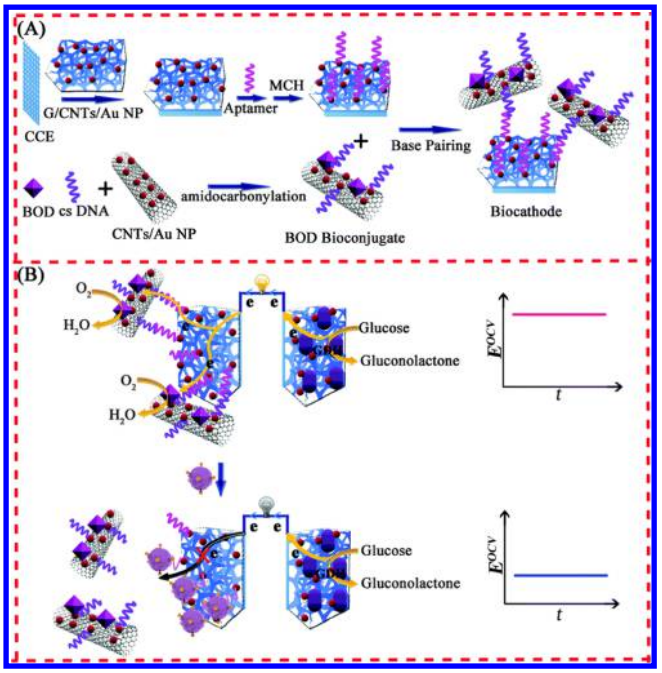


[a]Reprinted with permission from Meredith, M.; Minteer, S. D. Inhibition and Activation of Glucose Oxidase bioanodes for Use in a Self-Powered EDTA Sensor. *Anal. Chem.* **2011**, *93*, 5436−5441.[55].

selectivity problems due to the fact that there are many inhibitors of every enzyme, these sensors can have the high selectivity of the antibody, aptamer, or DNA hybridization based biorecognition element. For instance, Zhu et al. utilized a glucose/oxygen biofuel cell with an aptamer for cancer cells.[52] When the cancer cells bind, then it lowers the voltage and the power by blocking the binding of the oxygen reduction biocatalyst to the electrode, as shown in Scheme 2. Guo et al. have used this same strategy to prevent the binding of bilirubin oxidase at the cathode of a glucose/oxygen biofuel cell for sensing transcript factor protein p53 at pM concentrations.[53] Schuhmann et al. developed a competitive self-powered immunosensor for sulfonamide antibiotics where a lactose/peroxide biofuel cell utilizing a cellobiose dehydrogenase anode and an antibody modified cathode where a horseradish peroxide modified analyte analog competes with the analyte.[54] This resulted in detection limits as low as 2.4 ng/mL.[54] Overall, the blocking effect has resulted in highly sensitive and highly selective self-powered enzymatic biosensors.

Reactivation (sometimes called activation) based methods are another option. When an enzyme is inhibited, sometimes it

Scheme 2. Fabrication of Biofuel Cell and Operation of the Blocking Scheme[a]



[a]Reprinted with permission from Gai, P.; Song, R.; Zhu, C.; Ji, Y.; Wang, W.; Zhang, J.-R.; Zhu, J.-J. Ultrasensitive self-powered cytosensors based on exogenous redox-free enzyme biofuel cells as point-of-care tools for early cancer diagnosis. *Chem. Commun.* **2015**, *51*, 16763−16766.[52] Copyright 2015 Royal Society of Chemistry.

can be reactivated to make a turn-on self-powered biosensor versus a turn-off self-powered biosensor. For instance, although heavy metals (i.e., Cu^{2+}) frequently inhibit many oxidoreductase enzymes (i.e., glucose oxidase), the addition of EDTA can frequently reactivate those biosensors.[55] This transitions the turn-off sensors to a sensor where no EDTA results in no power, and as EDTA concentration increases, the power output increases. Therefore, transitioning to a turn-on sensor, as shown in Scheme 1. This same strategy has been used for a L-cysteine sensor where a FAD-dependent glucose dehydrogenase anode is inhibited by copper and then reactivated by L-cysteine, which turns the power back on to the glucose/oxygen enzymatic biofuel cell with a laccase biocathode.[56] Selectivity and sensitivity can range dramatically with these types of sensors.

Recently, enzymatic self-powered biosensors were expanded to hybrid self-powered biosensors by combining an enzymatic bioanode (glucose dehydrogenase oxidizing glucose to gluconolactone) with a nucleic acid biocathode that included a deoxyribozyme with an aptamer to design a logic gate.[15]

■ ORGANELLE SELF-POWERED BIOSENSORS

Analogous to enzymatic self-powered biosensors, organelle substrates could be sensed by organelle-based biofuel cells and biosolar cells. However, the sensitivity and selectivity of enzymes is greater, so there is not much point to developing these sensors. However, organelles are very sensitive to toxins. Therefore, inhibition-based sensors have been studied. For instance, mitochondria are inhibited by a variety of poisons and one of the main reasons that pharmaceutical drugs are taken off the market is because of long-term mitochondrial toxicity. Therefore, mitochondrial biofuel cells have been used to sense

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mitochondrial toxicity of substances ranging from poisons (pesticides and cyanide)[57] to drugs.[58,59]

Although most self-powered biosensors are biofuel cells, as described above in the introduction, they could be any galvanic cells. Therefore, solar cells could be included, since they have a positive open circuit potential and can generate power. Therefore, biosolar cells utilizing thylakoid membranes at the bioanode and oxygen reduction at the cathode have also been used as self-powered sensors, since the thylakoid membrane of the plant cell is inhibited by herbicides.[10] Again, these sensors have low selectivity, but are good for sensing toxicity to plants.

Both the biofuel cell and biosolar-cell based biosensors discussed above are inhibition (i.e., turn-off)-based sensors; organelle-based biofuel cells can also be reactivated. For instance, mitochondrial bioelectrocatalysis is inhibited by oligomycin (an oxidative phosphorylation inhibitor), but can be reactivated by an uncoupler. This means that mitochondrial biofuel cells produce no power in the presence of oligomycin, but are reactivated from uncoupling by nitroaromatic explosives. This allows for detection of nitroaromatic explosives down to 1 pM.[9] This sensor reacts to all nitroaromatic explosives, so it is not selective to an individual molecule, but a class of molecules, but this type of sensor can be very sensitive.

MICROBIAL SELF-POWERED BIOSENSORS

Conversely from enzymatic self-powered biosensors, microbial self-powered biosensors are not specific, or have very little specificity. However, this characteristic makes this type of biosensor extremely interesting for particular real world applications. As previously introduced, the development of microbial self-powered biosensors relies on the capability of microorganisms to exchange electrons with the electrode surfaces, which allow obtaining a microbial fuel cell (MFC). In a MFC, microorganisms transfer electrons obtained from the oxidation of substrates to the anode surface. The electrons flow to the cathode, throughout an external circuit, generating power. Accordingly, an easy to measure current/power signal is obtained.[60] Different concentrations of organic compounds, as well as the presence of toxic compounds that inhibit, or decrease, the activity of microbial cells can influence the power generation of the MFC. Thus, MFCs can be used as both a turn-on and a turn-off microbial self-powered biosensor. It has to be noted that MFCs were mostly developed as a power generation tool, and reports about their applications for biosensing purpose are less, but expanding in recent years. Remarkably, the first attempt to utilize a MFC as a turn-on self-powered biosensor for Biological Oxygen Demand (BOD) dates back to the work of Karube et al. in 1977.[61] The authors showed that utilizing a pure culture of *Clostridium butyricum* on the anode electrode of a two-chamber microbial fuel cell (called a "biological fuel cell" in their original work), a linear relationship between the steady state current and the BOD could be obtained, as shown in Figure 3A. Glucose, glutamic acid, and wastewater were utilized as substrates with good estimation of the BOD value, obtaining saturation of the signal only over 300 mg L^{-1} of BOD.

An important feature of microbial self-powered biosensors is their long operational stability. The continuous growth of new bacterial cells replacing old/dead cells, allows for the operation of the device in a very long time scale. Kim et al. reported another pioneering work, demonstrating a two-chamber MFC, inoculated with a mixed microbial consortium, operating continuously for over 5 years as a BOD sensor.[62] The

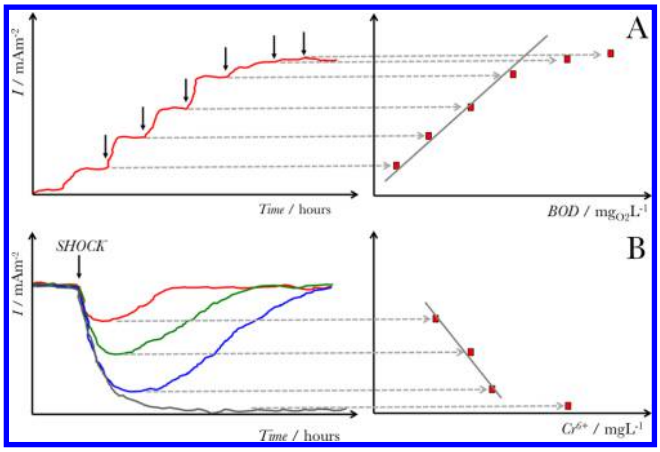

Figure 3. A. *i*–*t* curve for increasing BOD concentrations in a self-powered microbial biosensor (left), and corresponding calibration plot (right). B. *i*–*t* curve for increasing concentrations of Cr^{6+} shocks (left), and corresponding calibration plot (right).

generated current showed a quite limited linear response (up to 28 mg L^{-1} of BOD); however, utilizing the generated coulombs of charge passed, the linear range could be extended up to 206 mg L^{-1} of BOD. In the latter case, a long response time was required (~10 h), complicating the application in the field. Following these initial studies, different efforts have been focused on extending the linear range for BOD detection, lowering the limit of detection (the lower content of BOD that could be detected), simplifying the devices, and miniaturizing them for shortening the response time.[63,64] With these issues in mind, Di Lorenzo et al. developed a single-chamber MFC that could be operated in flow-mode. The small device (total volume 12.5 mL) showed a linear range of current response for the chemical oxygen demand (COD, which was corresponding to the BOD in their experimental setup), up to 350 mg L^{-1} in artificial wastewater.[65] Additionally, 40 min were sufficient for the small-scale device to reach a stable current output. The system was operated for up to 7 months, and the applicability with real wastewater was demonstrated. More recently, Di Lorenzo et al. developed a single-chamber MFC with 3D printing technology, which allowed further decrease of the total volume of the device to 2 mL operating in flow-mode.[66] Although the linear range of current response was lower than that of other studies (3–164 mg L^{-1} of COD), less than 3 min was required to obtain a steady state current response. The utilization of different membranes to decrease oxygen diffusion in the anodic chamber has recently attracted interest. A linear response up to 750 mg L^{-1} of BOD was achieved thanks to a sulfonated poly(ether ether ketone) membrane, that remarkably decreased oxygen diffusion at the anode, compared to the classical Nafion membrane.[67] Microliter scale MFCs (128–256 μL) were demonstrated with a natural and cost-effective membrane (an eggshell membrane), achieving good sensitivity, and remarkably extending the linear current response up to a BOD range of 9.8–4900 mg L^{-1}. Time for stable current output was decreased as short as less than 1 h, thanks to the high electrode surface-area-to-volume ratio, which ensured minimal differences in the concentration of organic substrate in the bulk and in the biofilm.[68] It is interesting to note that the applicability of MFC as self-powered biosensor has been recently demonstrated also in extreme conditions, where MFCs were utilized to monitor the degradation process of real oilfield wastewater.[69] By monitoring the produced coulombs of charge,

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the COD consumption could be estimated even with the high salinity (65 g L^{-1} of total dissolved salts) and complex organic molecules present in solution. Although the authors did not report a calibration plot, the applicability of MFCs in such a harsh environment represents an interesting starting point for future developments.

As previously introduced, microbial self-powered biosensors can be utilized also in turn-off mode, due to the inhibiting effects of different compounds on microbial activity. In this case, a MFC can be used for shock and toxicity measurements, as shown in Figure 3B. It is important to note that the MFC should be operating under saturating conditions, as changes in the current response must not be caused by a decrease in the concentration of available substrates. A "shock" event is defined as the occurrence of high loads of contaminants, such as heavy metals, in wastewater in concentrations orders of magnitude higher than the normal conditions. Although dedicated sensors might be used, the large variety of shocks would make this approach complicated. Accordingly, MFCs constitute an extremely interesting possibility for the detection of a broad range of analytes. In 2007, Kim et al. demonstrated that presence of toxic substances such as organophosphorous compounds, Pb, and Hg could be monitored by the decrease in current output of the MFC operated with synthetic wastewater.[70] The system was also able to operate with real wastewater, and shocks of cadmium and lead could be detected by an immediate decrease of the current output. The required time to recover stable operating conditions after the shock was proportional to the concentration of the toxic substance, ranging from 1 to 8 h. Particular efforts have been focused on improving the sensitivity,[71] determining shocks from different toxic compounds,[72,73] simplifying the devices,[74] and reducing the time required for the re-establishing of stable conditions after the initial shock. Microliter devices have been demonstrated, with an interesting report of filter membranes used as support for anode and cathode electrode, obtaining a MFC with a volume of less than 200 μL.[75] Impressively good linear response was obtained in a broad range of Cr^{6+} shocks (5−20 mg L^{-1}), but a long recovery time was required for shocks of more than 10 mg L^{-1} (80 h). An interesting approach to greatly increase the sensitivity was demonstrated by multianode MFC, using filter paper as support for conductive carbon ink.[76] Good stability (2 months of operation), fast response (<8 min), together with a high drop in power output were obtained (35-fold drop) for Cr^{6+} shocks, preventing false signals. Similarly, Jiang et al. reported a cathode-shared MFC, where four anodes were connected to the same cathode, separated by a cation exchange membrane.[77] The device was utilized for Cu^{2+} and pH shocks, as well as for the detection of organic matter. Although this setup allowed the biosensor to operate independently from variation in the cathode performance, a long recovery time was required after Cu^{2+} shock (10 h), complicating its application. The 3D printed MFC developed by Di Lorenzo et al. previously discussed for BOD monitoring was demonstrated also for Cd^{2+} shocks, with linear response up to 50 μg L^{-1}, requiring only 12 min to recover the baseline current after the shock event.[66] In a recent work, another approach to increase the sensitivity based on the transient-state operation of the MFC was reported.[78] Rather than maintaining the MFC continuously connected to an external load, Jiang et al. demonstrated that the selectivity could be increased up to 247% for Cu^{2+} shocks. The possibility to apply MFCs as a self-powered biosensor for volatile fatty acids, which are produced in anaerobic digesters, has also been demonstrated.[79,80]

Screen-printing technology has been applied in a recently published work to fabricate a paper-based microbial fuel cell.[81] Remarkably, the device is obtained utilizing fully biodegradable components. Specifically, carbon-based electrodes were screen-printed onto a sheet of paper, and the paper-MFC was demonstrated as a single use self-powered microbial biosensor for formaldehyde detection.

The presence of antibiotics in wastewater has raised concerns on the capability of classical biological processes to successfully remove this class of contaminants. Accordingly, recent efforts have been focused on the development of MFCs applied as self-powered biosensors for antibiotic toxicity detection. A single-chamber MFC equipped with $FePO_4$ nanoparticles-based cathode was demonstrated to generate a linear current response in the presence of Levofloxacin, an antibiotic of the fluoroquinolone family, in the range of 0.1−100 μg L^{-1}. Only 8 min was required to restore the baseline current, and the system was stable for 14 months of continuous operation.[82] A 13 mL single-chamber MFC was used as self-powered biosensor of tobramycin, another widely used antibiotic against infections. Linear response was obtained in a wide range (0.1−1.9 g L^{-1}).[83] However, many antibiotics are found in wastewater in μg L^{-1} concentration; thus, efforts should be focused on decreasing the limit of detection.

Among the challenges that microbial-based self-powered biosensors will have to overcome, the influence of external parameters is critical. In fact, changes in temperature or pH could affect the current/power generation, leading to erroneous evaluations. Moreover, for toxicity and shock monitoring, changes in BOD content might cause a false alarm.

LOGIC-GATE BASED SELF-POWERED BIOSENSORS

As discussed above, Boolean logic gates can be built into traditional sensors, as well as self-powered sensors. Joseph Wang, Shaojun Dong, and Evgeny Katz have been pioneers in this area. In 2009, Katz's group introduced the concept of combining biocomputing-based Boolean logic operations with biofuel cells and published an enzymatic biofuel cell with an AND/OR logic gate[84] and a biofuel cell that combined antibody-based biorecognition elements and enzymes to make a NOR logic gate in an enzymatic biofuel cell.[85] Several examples of enzymatic logic gates are shown in Figure 4.[86] Dong's group introduced in 2010 an AND logic gate.[87] This AND gate required three different enzyme inputs in a particular reaction order to generate power. Unlike most enzymatic biofuel cells utilized as a self-powered biosensor, this sensor was used to detect the enzymes as analytes and not the substrate/fuel. Her group extended this to substrates/fuels as analytes and developed an AND and a XNOR gate with a glucose/oxygen enzymatic biofuel cell.[88] Similarly to the enzymatic biofuel cell systems discussed above, these logic gate systems have also combined enzymatic bioelectrocatalysis with aptamer-based biorecognition.[89,90] Katz used the same combination of concepts to make a self-powered electrochemical memristor (memory-capable resistors).[91] Although there are many examples now of these and different logic gates being combined with biofuel cells, recently Wang and Katz have taken this a step further by designing "sense-act-treat" systems for using the biocomputing to decide when to release a drug delivery system.[92] This is a very exciting technology that will likely revolutionize how we think about self-powered biosensors and

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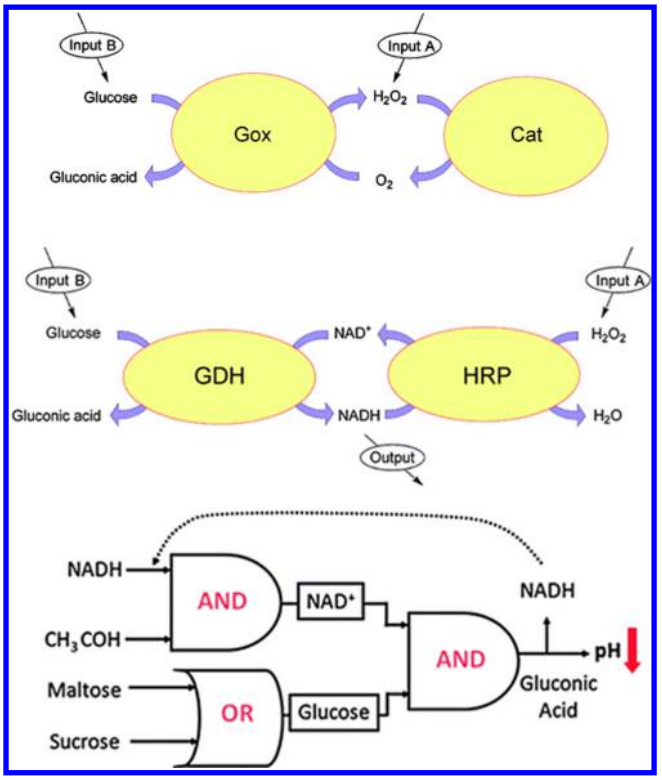

Figure 4. Examples of Enzymatic Logic Gates. (Top) AND Gate. (Middle) XOR Gate. (Bottom) Multigate system. Reprinted with permission from Katz, E.; Privman, V., Enzyme-based logic systems for information processing. *Chem. Soc. Rev.* **2010**, *39*, 1835−1857.[86] Copyright 2010 Royal Society of Chemistry.

their applications. Most examples of self-powered biosensors utilize enzymatic biofuel cells, but they can also utilize microbial fuel cells. For instance, Katz and Angenent developed an AND logic gate with a microbial fuel cell that has been used as a cytosensor.[11]

CONCLUSIONS AND FUTURE DIRECTIONS

When analytically evaluating self-powered electrochemical biosensors, it is important to compare their advantages and disadvantages to traditional electrochemical biosensors. The advantages include not needing a potentiostat including the circuitry and the power supply, higher sensitivity in many examples, and simplification by a 2 electrode design instead of a 3 electrode design. However, there are some disadvantages, including higher noise than a low potential mediated system[93] and more of a challenge designing mediators, because potential is so critically important. Currently, enzymatic self-powered biosensors have been designed with high selectivity, high sensitivity, and nearly instantaneous response time, but they are plagued with low stability due to attack from proteases and natural degradation. On the other hand, microbial self-powered biosensors have long functional lifetimes (>5 years of continuous operation), but they are plagued with low specificity and they typically have response times on the order of minutes to hours. Therefore, future research will need to address stability of enzymatic self-powered biosensors and response time and selectivity of microbial self-powered biosensors. These solutions could involve new cell designs, new materials, and new genetically engineered biological catalysts.

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Notes

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ABBREVIATIONS

Gox, glucose oxidase; GDH, glucose dehydrogenase; Cat, catalase; HRP, horseradish peroxide; ADH, alcohol dehydrogenase; MFC, microbial fuel cell; BOD, biological oxygen demand; COD, chemical oxygen demand

VOCABULARY

Biosensor, a device capable of providing quantitative, or semiquantitative, analytical information using a biological recognition element in contact with a transducer; Sensitivity, the change of measured signal per analyte concentration unit; Selectivity, indicates the characteristic of a sensor to respond selectively to a single, or a group, of analytes; Galvanic cell, an electrochemical cell driven by spontaneous chemical reactions that produce an electric current flowing through an external circuit; Biological oxygen demand, a standard method for measuring the amount of organic pollution, which can be oxidized biologically, present in a water sample. It corresponds to the amount of dissolved oxygen needed by aerobic biological organisms to decompose organic material present in a given water sample at certain temperature over a specific time period

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