Redox-active polymers in biofuel cells

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ABSTRACT

During the last decades, the possibility to produce electrical power from the chemical energy generated by biological catalysts has instigated remarkable advances in the field of biofuel cells. Biofuel cells use glucose primarily as a fuel and are highly relevant for powering portable, wearable and implantable electronic devices. Significant merit on this advancement is attributed to redox-active polymers that act as carriers for the enzymes while also "wire" their active site to the electrode surface. This chapter discusses in detail (the latest) trends in the chemistry, characterization, and application of redox polymers in biofuel cells. Firstly, the fundamentals of biofuel cells are outlined, along with a detailed classification of redox polymers. Finally, a thorough investigation of how redox polymers have been integrated in biofuel cell electrodes to yield power devices with promising performances is disclosed.

1.1. Introduction to biological fuel cells

The increasing cost of energy production, growing population, and environmental hazards that conventional fuels produce have made numerous research groups seek renewable, clean, and green alternatives to produce energy. Fuels such as waste biomass, solar energy, hydrogen, and biofuels are promising, sustainable energy resources that can fulfill the ever-growing energy demands of the world. Several “energy harvesting” technologies have been under development to convert locally available fuels into useful electricity. Biochemical energy harvesters such as biofuel cells (BFCs) are now justifiably regarded as one of the most promising renewable energy generation platforms as these devices can convert the energy of biological compounds into electrical energy. The catalysts of BFCs are often biologically abundant, such as catalytic enzymes or living cells, and the fuel is plenty as they are biologically relevant molecules (such as glucose or organic acids). The versatility of BFCs is attested by the different environments they can operate, including the human body (blood sugar), flora (tree-sap), or fresh, salt, and wastewater systems (biodegradable matter)¹. Since catalysts, fuels, and products are biologically derived and biodegradable, the inherent ecological aspect of BFCs compared to one of the conventional fuel cells is grand. BFCs do not require high temperatures for operation, which otherwise leads to the emission of nitrogen oxide gases mostly responsible for air pollution². Besides continuous power output typically independent of temperature gradients, BFCs’ main advantages are their simple design, use of renewable fuels and non-toxic electrodes and byproducts, reaction selectivity, and a moderately wide range of fuel choice.

There are two general classifications of BFCs in the literature. The first classification identifies a BFC as a device consuming a bio-fuel and/or bio-oxidant³.

The second classification is based on the definition of a BFC as a device comprising a biocatalyst such as a redox protein, an organelle, or living cells⁴. Since the former BFCs do not rely on biocatalysts, the second class of BFCs is also known as “biological fuel cells”. A biological fuel cell converges two-parent technologies, namely fuel cells and biotechnology. Fuel cells are galvanic cells that convert chemical energy into electrical energy⁵. The history of the fuel cell is dated back to Grove, who successfully reversed the action of the electrolysis of water in 1839 by recombining hydrogen and oxygen and produced electrical current. The link between biology and electricity - for BFCs, this link is established by the use of biofuel and biocatalyst in generating electrical power - has been made for the first time in the 1780s by Galvani who discovered that a frog’s leg could twitch by the current drawn from an electricity generator (**Figure 1a**). This experiment was not only a breakthrough for the understanding of the nervous system but also set the stage for Volta’s discovery of the electric battery⁶. Following these two discoveries, M.C. Potter, in 1910, observed electricity production out of an *E. coli* culture, establishing a new type of fuel cells now known as “microbial fuel cells.” The discovery was followed by Cohen et al., who reported a voltage output higher than 35 V by connecting multiple microbial fuel cells in series,⁶ along with the demonstration of the first BFC using a cell-free enzyme in 1964 by Yahiro et al⁷. In the 1960s, BFCs were built incorporating enzymes and, for the first time, electron mediators, which facilitated mediated electron transfer (MET) between enzymes and electrode surfaces. The next breakthrough came in 1978 when Berezin et al. developed a BFC that exhibited direct electron transfer (DET)⁸. In 2001, Heller et al. built a micron-scale BFC from single carbon fiber as the microelectrode drawing power from bodily fluids, revealing the potential of BFCs as power sources for bioelectronic devices⁹. The development of nanostructured electrodes based on high-

performance materials such as graphene has been a milestone for BFC technology. These electrodes enabled an increased surface area for enzyme loading as well as their stable immobilization while promoting the occurrence of DET¹⁰. The BFCs with typical power densities of a few tens of $\mu\text{W cm}^{-2}$ reached up to ca. 2 mW cm^{-2} with the incorporation of carbon nanotube (CNT) and graphene-based electrodes¹⁰. Ever since, research focused on improving the power density and lifetime of devices through various enzyme immobilization techniques, electrode materials, and cell designs^{1,11–13}. Due to lower electrical power that BFCs generate compared to conventional fuel cells, the scope of applications is limited for BFCs, at least for now. Their power output fulfills the needs of low-power electronics such as implantable, miniaturized medical devices, e.g., sensors and actuators¹⁴. For these applications, the BFC acts as a biobattery that finds the biofuel either contained in one of its compartments or fed through a flow-through system from the biological environment¹⁵. Despite these flexible design features, the major drawback of BFCs is associated with their lifespan, mostly limited by the environmental instability of immobilized enzymes¹⁵.

BFC operation is similar to that of conventional fuel cells. During a typical fuel cell operation, oxidation occurs at the anode when the catalyst interacts with its substrate. This reaction releases electrons, which travel to the cathode via the external circuit, generating electrical work. The circuit is completed when a compensating charge, often in the form of a cation, moves through the electrolyte to the anode. Typically, fuel cells use small molecules such as hydrogen, ethanol, and methanol as fuel (the substrate of the redox reaction) and produce energy, water, and carbon dioxide¹⁶. BFCs, on the other hand, find their fuel directly in bio-fluids where it is readily abundant, independently replenished, and cost-effective. We can categorize three biofuel cell configurations, namely microbial, enzymatic, and non-enzymatic biofuel

cells, where the former two are also known as biological fuel cells (**Figure 1b**). Microbial fuel cells make use of entire living cells or microorganisms comprising redox intermediates which catalyze the oxidation of a particular fuel¹⁷. Enzymatic BFCs catalyze chemical reactions by use of specific redox enzymes, i.e., catalytic protein that can be extracted and purified from suitable living organisms. The enzymatic or microbial fuel cells have thus no toxicological, explosive, or flammable risks⁶. Non-enzymatic fuel cells, on the other hand, use platinum alloys or activated carbon as catalysts. Still, the electrochemical reactions that they drive are inside a living cell, i.e., *in-vivo*, hence relying on biological fuels¹⁸. In this chapter, our focus will be on the enzymatic BFCs, in particular, those that use glucose and oxygen (O₂) as their fuel.

Enzymes (alone or within an organism) are globular proteins that contain reaction sites that catalyze biological reactions in the body. They are preferred over inorganic catalysts as they are biocompatible, renewable, show higher efficiency and activity at mild pH and temperatures, and superior substrate selectivity¹⁹. Enzymes work with cofactors such as quinones, flavins, and nicotinamides to assist in the catalysis of specific reactions, shuttling of electrons, protons, or hydrides²⁰. They achieve high catalytic turnovers at mild conditions (i.e., 25-35°C and pH 5-8). They apply selectively to a variety of fuels that do not require processing steps given that impurities in the fuel do not passivate the catalysts. The high specificity of enzymes towards their substrates allows the anode and the cathode to operate in the same compartment, rendering the devices easy-to-assemble and miniaturize. However, enzymes are labile constituents as they easily degenerate if exposed to environments with conditions differing from their native habitat.

A class of electronic materials that have shown promise to couple with enzymes in BFC electrodes are redox-active polymers. Besides their redox activity (i.e., ability

to accept and transfer electrons/holes of an enzymatic reaction), these materials show a unique set of features such as synthetic tunability, biocompatibility, hydration, modifiable surface energy, porosity and charge transport (valid for those that have conjugated backbones). These properties are ideal for exploiting the construction of high-performance BFC electrodes. In this chapter, we will discuss challenges as well as the opportunities of redox polymer-based enzymatic BFCs. We will first provide an overview of the operation principles, components, and characterization of enzymatic BFCs. We will then discuss the types of redox-active polymers applied in enzymatic BFCs, the charge transport properties of these polymers, and the function of enzyme integrated electrodes. Finally, we will showcase the performance of a selected set of polymeric BFCs and summarize the state-of-the-art advances in the field with a perspective on the challenges associated with their practical use.

1.2. Fundamentals of BFCs: components, operation, and characterization

1.2.1. BFC configuration

The typical components of biofuel cells are analogous to those of the conventional fuel cells. In the simplest form, two electrodes with appropriate work functions are functionalized with enzymes and placed in an electrolyte that contains the fuel (**Figure 2a**). Classical BFC configurations comprise an ion-conducting membrane or a salt bridge between these two electrodes, which separates the anode from the cathode²¹. Such cells operate in either batch or continuous mode. The incorporation of a membrane is essential to isolate the reaction of the enzyme with the substrate at the surface of its corresponding electrode. The membrane controls the transport of the chemical species (e.g., fuel, O₂, and byproducts) involved in the chemical reactions in the solution across the two sides of the BFCs. Membrane material should be carefully selected since the transfer rate of the investigate species

affects the performance of the BFC¹. In a BFC, fuel is supplied to the anode and gets either partially or fully oxidized by the biocatalyst therein, leading to the release of electrons (**Figure 2a**). The electrons travel to the cathode where the oxidants, e.g., O₂ or peroxides, are reduced to water^{22,23}. The electrode material at the cathode can either perform this reduction reaction by itself or is complexed with an enzyme that catalyzes this reaction. The outcome of these reactions is captured as an electrical current or potential.

BFC electrodes must possess high electrical conductivity alongside the physicochemical properties at the surface favored by the enzyme to ensure interactions that keep them in proximity for long periods. A high surface area is desirable for a high enzyme load, while the electrode has to facilitate efficient mass transport of fuels and oxidants^{3,24}. Some of these requirements have been fulfilled by mesoporous structures in the form of nanoparticles (NPs), nanotubes, and nanocomposites. Exhibiting such architectures, carbon-based materials (carbon paper, carbon nanotubes (CNTs), graphite, and carbon cloth) are the most widely used electrode materials in BFCs²⁵ due to their high porosity, conductivity, low-cost, biocompatibility, thermal and chemical stability, ease of functionalization and robustness^{3,26}. For instance, CNT-based “Bucky paper” is now commercially available, and another carbon-fiber paper, i.e., “Toray paper,” has been employed displaying seamless electronic communication with enzymes because of its high conductivity and porosity^{27,28}. These electrodes can be further functionalized with redox-active polymers, as discussed in Section 1.3.

Note that because of the high specificity of enzymes towards their substrates and their activity compatible with mild pH conditions and intermediate ionic strengths, BFCs can sustain operation without a membrane^{29,30}. Thus, some BFC configurations

have obviated the need for membranes (*i.e.*, one-compartment design) as they can avoid crosstalk (shorting) between the anode and cathode²¹. In 1999, Katz, Willner, and coworkers reported the first membrane-free glucose/O₂ BFC³¹, and numerous other demonstrations have followed ever since (see **Table 1** for bioelectrodes and **Table 2** for membrane-free BFCs made thereof)^{11,21,32}. The simplicity of assembling all the cell components in one platform is advantageous for miniaturization, shifting the focus towards the development of implantable platforms.

1.2.2. Enzyme Immobilization

Efficient energy conversion in a BFC depends on the biocatalytic performance of the anode and the reduction capacity of the cathode (typically for O₂ reduction reaction). The bioanode of a BFC defines an electrode functionalized with the catalytic enzyme. The enzyme should be effectively immobilized on the electrically conductive support material selected and, at the same time, preserve its native conformation to ensure long-term stability³³. For bioanodes comprising electron mediators, the enzyme and the mediator ought to be effectively immobilized at the electrode surface to provide rapid electron transfer rates, decreased enzyme leaching, and mitigation of diffusion limitations³⁴.

Once attached to their corresponding electrodes, enzymes have efficient channels for electronic communication with the underlying conducting material to achieve high power densities³³. In the immobilized form, they are more resistant to changes in environmental conditions such as pH and temperature compared to when they are freely diffusing in electrolytes. During immobilization, one of the major concerns is the denaturation of the enzyme. Enzymes have their catalytic centers typically curried inside their insulating shell. The denaturation of the enzyme involves a transformation of the natural 3D, globular form of the protein into an extended

conformation. During this change of conformation, the catalytic centers come closer to the electrode (desired for electrode-catalytic center interactions). However, they get exposed and, in turn, unprotected in this new environment, which can lead to a loss in their activity and subsequently complete dysfunction.

Successfully reported strategies for immobilization/integration of enzymes on solid supports are physical adsorption, covalent binding, cross-linking, layer-by-layer encapsulation, and embedding/entrapment (**Figure 2b**)³⁵. With these strategies, a randomly oriented enzyme layer is formed, either on the surface of the electrode or inside the cavities of an encapsulating matrix or of the electrode itself (given that it is highly porous). Physical adsorption occurs when intermolecular forces between the electrode surface and the enzyme lead to the accumulation of protein(s) therein. Since these interactions are based on weak van der Waals forces, the reasonable approach to ensure long-term enzyme adhesion to the surface is to increase the number of contacts between the surface and the enzyme. This method is simple because no reagents or surface functionalization are required. The enzyme can, too, be covalently linked to the electrode surface if the latter has reactive groups (such as amides, sulfurs, or carboxylic acids). Enzymes are cross-linked inside a network, a process building covalent bonds formed typically within and between encapsulating polymer networks and the electrode surface or membrane-like matrices and the enzyme. Bunte et al. developed a redox polymer containing cross-linkable benzophenone groups, that entrapped the enzyme inside the network during photo-induced crosslinking³⁶. This approach may result in lower enzyme/electrode contacts, yet it provides stability. Enzymes can be physically embedded in sol-gel like matrices, which are then cast on electrodes. The enzyme layers are cast sequentially in-between charged polyelectrolyte layers, forming a multi-layered assembly of enzymes embedded in

between polyelectrolyte films. Even at a bilayer configuration, the encapsulation of polymers can prevent the leakage of enzymes. Xiao et al. utilized a poly(acrylic acid) coating layer on a glassy carbon electrode coated with an Osmium (Os) redox polymer and lactate oxidase, and found an improved catalytic response for high substrate concentrations³⁷. Lastly, the use of conducting polymers as electrode coatings is closely linked with entrapment techniques. Entrapment entails the polymerization of a monomer (typically, electropolymerization) in the presence of the protein, which results in an entrapped protein inside the conducting polymer network³⁴.

The immobilization methods summarized above trade stability for enzyme activity. Chemical bonds formed between the enzyme and a given surface or even physical interactions that are weaker might alter the enzyme structure, hence its function, and affect the electron transfer rates when the orientation of the catalytic center is not preserved. Yet, immobilization results in an improved lifetime as the enzyme cannot readily de-link itself from the electrode and remains protected from other species that may be present in the electrolyte. When choosing an enzyme immobilization strategy, the nature of the particular enzyme and the underlying substrate have to be evaluated. The chemical groups and the charge on the enzyme surface, the size of the enzyme as well as its 3D polarity distribution (hydrophobic/hydrophilic regions) has to be considered³⁸. Substrate charge, roughness, and polarity should be optimized to ensure high enzyme loading and combat leaching. Finally, the properties of the environment where enzyme immobilization takes place must be compatible with the enzyme.

1.2.3. Electron transfer mechanism in BFCs

For a high-power density BFC, there should be an efficient mechanism to rapidly transfer the electrons generated by the catalytic center of the enzyme where

the reaction with its substrate takes place. The way that the protein conforms itself on the electrode and the positioning of its catalytic centers determine the electrical coupling with the electrode and in turn the performance of the BFC.

Two main approaches are envisaged in the quest for effective coupling between the enzyme and an electrode: the direct and the mediated (indirect) electron transfer (**Figure 2c**). Electron transfer (ET) occurs through Marcus-type collisional electron transfer wherein individual redox centers move within short distances and come close enough to one another to facilitate outer-sphere self-exchange reactions³⁹. The rate at which electrons move through the enzymatic film limits the overall communication between the enzyme and the electrode³⁹. Direct electron transfer (DET), i.e., the tunneling of electrons from the redox-active catalytic center of the enzyme to the electrode surface directly⁴⁰, can be established if the enzyme is in the proximity of the electrode (see **Figure 2d**, biocathode). In this case, the enzyme is positioned in a manner that its active site is oriented towards the electrode, ensuring that its distance to the electrode surface is as short as possible. Dutton and co-workers provided a rule-of-thumb for the occurrence of DET within metalloenzyme structures that an electron tunneling distance of less than 14 Å between redox-active sites supports sufficiently fast ET rates and is required so as not to limit the rate of redox catalysis⁴¹.

Bioelectrodes which rely on mediated electron transfer (MET) contain a low-molecular-weight, redox-active species, known as a mediator (**Figure 2c**). The mediators are used to shuttle electrons between the enzyme active site and the electrode (see **Figure 2d**, bioanode). They increase the rate of electron transfer between the active site of the enzyme and the electrode, and as such, the stringent electrode design requirements of DET are mitigated. In this case, the enzymatic reaction catalyzes the oxidation or reduction of the redox mediator, and the reduced

mediator is simultaneously regenerated on the electrode surface⁴². The mediator (e.g., ferrocene, Prussian blue, methyl viologen) must possess a redox potential close to that of the enzyme cofactor to transfer electrons rapidly upon application of a low voltage (**Figure 2e**). For efficient current collection, electron transfer from the enzyme to the mediator should be at least as fast as the transfer of electrons from the metabolite to the enzyme. Due to their typically small size, the freely moving redox molecules can readily interact with the cofactor, enhancing the fuel cell performance. Yet, the addition of mediators into the system comes with issues such as mediator leaching over time and increased complexity of the electrode design to immobilize the mediator.

The ET events from the active site of an enzyme to the electrode surface or the immobilized redox-active molecule can be either intermolecular or intramolecular. In the intermolecular case, the enzyme acts as a freely-diffusing but high molecular weight redox mediator. For the case of intramolecular ET, the attached redox mediator swings in and out of the active site of its enzyme. The ET rate depends on the interfacial electron transfer rate and the turnover number of the enzyme¹⁹. A BFC electrode can be assembled from electronic materials that perform DET with enzymes or involve mediators (**Figure 2d**). The selection criteria of these materials concern the careful alignment of the energetics of enzymatic reactions and redox-active components. Apart from establishing ET pathways, the design should consider mass transfer processes involved in the BFC reactions, all subject to transfer limitations. These processes can set limitations to the performance of the BFCs and ought to be optimized through careful consideration of device geometry and materials used.

1.2.4 BFC characterization and figures of merit

The performance of a BFC is determined in terms of power output, voltage, and current¹⁹. Typically, linear sweep voltammetry or chronoamperometry is implemented to characterize the BFC performance and to monitor the response of the whole device or the half-cells (anode and cathode, individually). These electrochemical techniques reveal several vital parameters, including onset potentials of the redox reactions, ohmic losses at the electrodes, the maximum current extractable from each electrode, and the theoretical open-circuit voltage. A standardized methodology for testing BFC performance and reporting figures of merit is indispensable for comparing and benchmarking BFCs in terms of electrode and mediator performance, and configuration. However, the experimental approaches differ in 1) the specific surface area or volume of the electrode, 2) mass transport of the fuel to the surface, 3) coverage, thickness, density and activity of the enzyme or the mediator on the electrode surface, and 4) stability of the system. Other differences include variations in operational conditions such as pH, ionic strength, electrolyte composition, and concentration, temperature. The reports in the literature involve different techniques to determine current output (such as amperometry, cyclic voltammetry at different scan rates or measurements directly in the BFC configuration) and power density (i.e., fixed load, potentiostatic or galvanostatic control)⁴⁵.

The open circuit voltage (OCV) of the cell is one of the most important BFC figures of merit. It is defined as the voltage output of the BFC when there is no external electric current between the electrodes. OCV depends on the solution composition and follows the Nernst equation⁴⁶:

$$E = E^o - \frac{RT}{nF} \ln Q \quad (\text{eq. 1})$$

where Q is the transported charge, E is the cell potential, R stands for the universal gas constant, T is the absolute temperature, n is the number of electrons involved in the reaction, and F is the Faraday constant. The OCV is determined from the difference between the thermodynamic potential of the fuel/oxidized product redox couple (half-reaction of the anode) and of the oxidant/reduced product redox couple (half-reaction of the cathode) (**Figure 3a**). The difference between the open-circuit potential of the biocathode and the bioanode determines the electrochemical driving force. The difference between the OCV and the apparent standard redox potential of the catalyst (E^0), that is, the overvoltage (η), defines the deviation of catalyst from ideal and is thus a measure of its efficiency (**Figure 3a**)⁴⁷. From a thermodynamic point of view, the electrochemical efficiency of the cell is expressed by¹⁵:

$$Efficiency = \frac{-nF\Delta E}{\Delta H} \quad (\text{eq. 2})$$

in which ΔE is the potential difference between anode and cathode, and ΔH represents the enthalpy variation as the anodic reaction occurs ($\Delta H = n \times F \times \Delta E$). This efficiency is lower than the one in practice, meaning that the measured OCV is not determined solely by the thermodynamics of the reactants and is much lower than the theoretical value of ΔE . This discrepancy arises due to the presence of three types of loss channels: kinetic factors related to the overpotentials for the corresponding reactions at the electrode/electrolyte interface, mass transport due to reactant diffusion limitations, and ohmic losses associated with all the resistances in the system¹⁹. In a typical BFC polarization curve (**Figure 3b**), the measured value of OCV is lower than the theoretical one, the latter determined by the analysis of the individual half-cell responses (**Figure 3a**).

Three mass transfer processes are involved in the BFC reactions, all subject to transfer limitations. A rapid fall in the voltage occurs, followed by a smoother and less rapid decline. Although the former is attributed to kinetic parameters caused by a slow rate of reaction at the electrode surface, the limiting second phase is because of resistive (i.e., ohmic) losses. Resistive losses are ascribed to the resistance of electrons through the electrode materials and that of ions through the electrolyte. At the final stages (i.e., higher currents), the voltage falls faster due to the system being mass transport limited. Mass transport limitations arise as the concentration of the reactants on the electrode surface changes with more fuel consumed. Finally, the OCV of glucose/O₂ BFCs lies below the thermodynamic limit of 1.18 V^{47,48}. BFCs with MET-based electrodes have thermodynamic losses due to the presence of mediators, leading to a smaller cell voltage (recall **Figure 2d**).

The other figure of merit of BFC performance evaluation is its power, depicted in **Figure 3c** and expressed as⁶:

$$P_{cell} = E_{cell} \int J_{cell} dt \quad (\text{eq. 3})$$

where E_{cell} stands for the cell voltage, and J_{cell} is the cell current. The commonly used electrochemical technique to determine P_{cell} is the polarization at variable load resistances or slow scan-rate (<0.1 mV s⁻¹) cyclic voltammetry. Investigating each electrode separately (the half-cell data) allows identifying the electrode that limits the electrochemical reaction; hence, the J_{cell} ¹⁹. The current output can be improved by adopting the appropriate immobilization strategy and promoting the mass transport of reactants and products¹⁹. Under closed-circuit conditions, the measured E_{cell} is defined as¹⁹:

$$E_{cell} = E_C - E_A - \sum IR_{ohm} \quad (\text{eq. 4})$$

in which E_C and E_A are the experimental cathode and anode potentials, respectively. These potentials are related to the equilibrium potential (E_e) by the following equation⁴⁹:

$$\eta = E - E_e \quad (\text{eq. 5})$$

Here, the difference between the resultant potential E and E_e is called polarization. This difference is quantified in terms of an overpotential (η), i.e., the additional potential (beyond the thermodynamic requirement) required to drive an electrochemical reaction at a certain rate. To maximize the OCV, it is instrumental to bring the starting potential of the electrodes closer to those of the enzymes/mediators so as to lower the overpotentials (see **Figure 3a**) (i.e., the difference between the redox potential of the enzyme and that of the electrode)⁴⁴.

The maximum electrocatalytic current (or maximum power, $P_{\max}$, **Figure 3c**) is the highest power that the fuel cell can achieve. It depends on the density of active catalytic sites and the reaction rate at each active site, which is linked to the turnover number of the enzyme¹⁹. The power density (PD) of the BFC is expressed as¹⁹:

$$PD = \frac{P_{cell}}{A} \quad (\text{eq. 6})$$

where A is the geometric area of the electrode. Maximum power density (MPD) of a BFC is the $P_{\max}$ normalized by electrode area.

Overall, the BFC performance is correlated to the ET efficiency between enzyme and electrode surface, which regulates the current, and the potential difference between the bioelectrode pairs that, in turn, dictates the OCV. The biggest hurdles of enzymatic BFCs thus lie in the low power output stemming from impaired electron transfer and mass transfer limitations and the unmatching cathode and anode

potentials. The concentration overpotential is caused by the slow mass transfer rates of reactants and reaction products. Ohmic losses stem from the resistance of the ions that flow in the electrolyte, the impaired proton transfer through the membrane, and the slow flow of electrons through the electrode⁵⁰. The OCV can be improved by maximizing the driving force ($E_C - E_A$) and mitigating the ohmic resistance losses through improved cell design, such as those with narrower inter-electrode gaps^{19,24}.

It is important to understand the origin of losses in BFCs in order to extract design rules for next generation devices. Techniques such as infrared microscopy can be implemented to investigate the molecular composition within the localized regions of BFC electrodes⁵¹. An in-depth assessment of the structure and intermolecular interactions among the components, changes in enzyme conformation upon the operation, and in its microenvironment will provide insights into loss mechanisms in BFCs that remain unknown.

1.3. Redox-active Polymers

Redox-active (or, simply, redox) polymers are macromolecules which contain certain chemical groups that can reversibly change their electrochemical state by losing (oxidation) or gaining (reduction) electrons. They allow to co-immobilize enzymes and redox mediators on the electrode surface. To this end, redox-active polymers are responsible for managing the transfer of both ions and electrons that are generated as their redox-active units interact with substrates. They differ from inorganic electrode materials as they are softer and do not require ions to intercalate into the solid-state structure⁵². Compared to isolated, freely moving redox couples, redox-active polymers covalently immobilize the redox centers, providing stability. Redox properties are governed by the nature of the polymer backbone (conjugated or non-conjugated) and the

properties of spatially localized redox groups if (they are present)⁵³. When combined with biocatalysts, such as enzymes and living cells, redox polymers have not only been used in BFCs but also for biosensing, biophotoelectrochemistry and bioelectrocatalysis applications⁵⁴.

The synthesis of redox polymers involves the typical main steps of polymerization, namely, initialization, propagation, and termination. An initiator molecule introduced to the reaction mixture triggers the polymerization reaction by reacting with a monomer, attacking its double bond, and forming an unstable-reactive species (i.e., monomer radical). The latter forms another bond with a monomer, sequentially yielding a long chain of monomers, called the macro radical. The reaction is terminated by a chemical reaction that ceases the formation of reactive intermediates. The length of the chains and their polydispersity affect the chemical, electrical, and physical properties of the polymer film. The simplicity of the polymer synthesis, as well as its processing into the final form, is essential for its use as a BFC electrode coating since the polymer and the devices made thereof can be easily scaled-up.

Redox polymers transport charge either via a mediated electron transfer through the redox relays or electron hopping mechanism through the polymer (conjugated) backbone (**Figure 4a**)^{55,56}. They constitute a hydrated electron-conducting system that supports the diffusion of ions, substrates (glucose, O₂), and products. The redox relays bound to the polymer backbone can be of organic or inorganic/organometallic origin^{55,57}. The electrons that are generated in one enzyme-linked redox unit of the polymer are transferred to another redox unit through collisions between them. If the redox moiety possesses low reorganization energy, the self-exchange rate is fast⁵⁵, like in the case of Os complexes^{58,59}. Here, if the

polymer backbone is conducting (i.e., conjugated), the redox-active polymer could act as a molecularly conducting wire combining high redox activity of dedicated redox sites with electronic conductivity. A prime example is the electron-transporting polymer, poly{[N,N'-bis(2-octyldodecyl)-1,4,5,8-naphthalenedicarboximide-2,6-diyl]-alt-5,5'-(2,2'-bithiophene)} (P(NDI2OD-T2)) (**Figure 4a**)⁵⁶. Most commonly used conducting polymers in BFCs are however hole-conductors. Polypyrrole (Ppy), polyaniline (PANI), and polythiophene are p-type polymer which are typically electropolymerized as films on conductive substrates. While supporting charge transfer, they act as a matrix wherein the enzyme is immobilized⁶⁰.

1.3.1. Classification of redox-active polymers

Redox-active polymers can be categorized under two groups depending on the location of the redox-active center in the chemical structure: 1) redox-active group embedded polymers and, 2) redox-active pendant bearing polymers, as depicted in **Figure 4b**⁶¹. In the first group, the redox units are integrated directly to the backbone, while in the second group, they are grafted to the backbone as pendant side chains. The majority of redox polymers of group 1 have π conjugation in their backbone (an alternation of single and double bonds where sp^2 hybridization gives rise to weak π -bonds and reduced bandgaps), which provides them with a semi-conducting character. Polarons and bipolarons can propagate an electrical current along the polymer chain as charges hop along the molecule through delocalized π -orbitals, and between molecules which exhibit sufficient π - π overlap⁶². Likewise, sulfur polymers belong to group 1, are highly redox-active but they are not conducting polymers⁶¹. They have sulfur-sulfur bonds (-S-S_n-S-) embedded in a non-conjugated polymer backbone, such as poly(sulfur-random-(1,3-diisopropenylbenzene))(poly(S-*r*-DIB))⁶¹. During the redox process, conjugated, redox-active polymers grant the charge to travel

across their chains (**Figure 4a**), leading to electronic communication between redox centers, as well as a shift of the redox potential that would otherwise be expected for the isolated redox centers⁵³. Another classification comes from the nature of the redox-active molecule, either organic or inorganic. Overall, these classifications always include exceptions as hybrid forms exist due to the large variety of redox-active polymers that have been developed thanks to the syntethic tunability inherent to polymers⁶¹.

1.3.1.1. Redox-active group embedded polymers

Figure 4b shows the chemical structures of some of the most common redox-active group embedded polymers with a conjugated backbone, namely, polyaniline (PANI), poly(3,4-ethylenedioxy thiophene) (PEDOT), poly(3,4-propylenedioxy thiophene) (PProDOT), polythiophene (PT), and polypyrrole (Ppy)⁶¹. Polyacetylene (PA), poly(indole) (PI), and poly(*p*-phenylene) (*P-p*-P) are other redox-active polymers that belong to this group⁶⁴. The similarity of these chemical structures with biological compounds is promising for the activity of the biocatalyst coupled to the polymer film. The electrochemical properties of conjugated polymers depend on their molecular weight, morphology, degree of doping, and the nature of dopant ions⁶¹. These polymers typically undergo redox reactions upon interaction with electrolyte ions transported by an electrical field.

Conjugated polymers can be doped to be p-type (i.e., hole transporting) and n-type (electron-transporting) semiconductors. P-type doping suggests the oxidation of the polymer, leading it to gain a positive charge (in the form of a hole). In contrast, n-type doping occurs when the polymer is reduced and thus possesses a negative charge (i.e., an electron). The n- and p-type character can be controlled by the

engineering of HOMO/LUMO levels with electron-rich and poor moieties in the backbone. Heavily and slightly doped p-type doped polymers such as Ppy, PEDOT:PSS, PANI, PEDOT, and PT are stable under ambient conditions⁶¹, unlike most of the n-type conjugated polymers. The difficulty in arriving at a durable n-type material arises from the instability of organic anions, especially carbanions that are oxidized in air and water. To have high stability, the material should have a deep LUMO lower than -4.0 eV⁶⁵. A more rigid backbone has shown to improve charge transport.

Charge carriers are introduced into the conjugated polymer by doping, either chemically or electrochemically. In chemical doping, there is a direct charge transfer from an oxidant to the polymer, such as the case of PANI getting protonated by acids. Electrochemical doping, on the other hand, requires the application of a voltage on a conjugated polymer film through an electrolyte. The process entails the following elementary steps; electronic charge injection from the metal electrode into the polymer, charge transport across the adjacent localized states, ion injection from the electrolyte into the polymer, ion transport in the free volume between the polymer crystallites or chains, and electrostatic compensation of the two charges in the bulk of the film⁶⁶.

Faradaic charging of a conjugated polymer film implies a current arising from oxidation/reduction reactions happening at the backbone. The CV curves of a conjugated polymer film coated on a conductive substrate display Faradaic and capacitive processes (**Figure 5a**)⁶⁶. The CV measures the outcome of a chain of events associated with mixed ionic and electronic conduction that may involve morphology changes, delocalized states, and multiple charge compensation (doping) mechanisms⁶⁶. Therefore, CVs are not particularly conclusive in determining the redox

activity of conjugated polymer films. A typical figure of merit for polymers that can be delineated from CV or galvanostatic charge-discharge is the capacitance, which is the ability of the polymer film to store charge for a given voltage. For certain polymers, however, the CV curves display discrete features reflecting electron transfer processes localized on single repeat units, stabilized with a cation or anion supplied from the electrolyte⁶⁷. Naphthalene1,4,5,8-tetracarboxylic-diimide-alkoxybithiophene (NDI-T2) based n-type polymers, for instance, show distinct features of reduction and oxidation couples in their CV curves and an abrupt change in the film conductivity around the voltages that correspond to the reduction reactions (**Figure 5b-c**)⁶⁸. Such Faradaic behavior is possible to observe in CVs if the charge localizes on an individual repeat unit as it does for P(NDI2OD-T2) in **Figure 5b**. The NDI unit undergoes a reversible and rapid doping/de-doping process with Li ions, making this polymer promising to form fast rechargeable Li batteries⁵⁶. Another commonly used redox polymer is PEDOT (the most common form of this polymer is PEDOT doped with polystyrene sulfonate, PEDOT:PSS) with its dominating capacitive behavior. PEDOT acts as an O₂ reduction catalyst in its de-doped form, and gets re-oxidized and reduced reversibly upon its interaction with O₂ dissolved in aqueous electrolytes^{69,70}. As such, this polymer is a strong candidate for a BFC cathode.

1.3.1.2. Redox-active pendant bearing polymers

In this type of redox-active polymers, the redox-active units are attached to the polymer backbone by a tether. The redox units can be either of organic (such as quinones or viologens) or organometallic/inorganic (such as Os, ferrocene (Fc), or cobaltocene) origin. An array of redox-active pendant-bearing polymers, mostly on non-conjugated polymer backbones, have been reported. The functional groups

include carbonyl compounds, viologen, organosulfur, Fc, quinones, and radical compounds such as nitroxyl, phenoxyl, and verdazyl groups (**Figure 4b**)^{61,71–73}. These polymers exhibit a wide electrochemical window depending on the redox units that they possess. The reversible oxidation/reduction potential of common redox couples, deduced from cyclic voltammetry experiments, are displayed in **Figure 6**⁵⁷. The redox potentials depend on experimental parameters, such as the electrolyte type and ionic strength, and cell configuration. Although they show high redox activity, the low electrical conductivity of this class of redox polymers due to their insulating backbone necessitates the use of conducting materials in conjunction with these polymers.

These variations in redox potentials make redox polymers advantageous to use in enzymatic BFC electrodes. Ideally, the redox polymer must possess a redox potential close to one of the enzymes and can be adjusted by choice of redox unit. For instance, the formal potential of the Os-complex bearing redox polymers can be tuned by choosing different combinations of ligands (changing the substituents therein) in the octahedral complex, which modifies the electron density of the central Os center⁷⁴. Moreover, the concentration of the selected redox unit alongside the composition of the polymer backbone, chain length, and the spacer that connects the pendant unit to the backbone, can be tailored to fulfill the needs of the biocatalyst and the reaction.

Typical ways to polymerize and introduce redox-active groups to the monomers include polycondensation, oxidative polymerization, and free-radical polymerization. Recent works have also employed anionic polymerization, atom-transfer radical polymerization, and reversible addition-fragmentation chain transfer polymerization⁶¹. The most common synthesis route for these polymers is the “ligand exchange method,” as well as the covalent binding approach of the (metal) redox complex already bearing the suitable ligand⁷⁵. Poly(N-vinylimidazole) (PVI) or poly(4-

vinylpyridine) (PVP) are typical backbones to tether redox units⁴⁵. The success of organometallic compounds as redox components has led to the development of more advanced versions where new synthetic routes have been developed (such as the epoxide opening reaction⁷⁵) to enable the immobilization of the enzyme on the redox-polymer surface^{38,57}. More recently, Os complexes that bear chelating N-heterocyclic and bipyridine ligands were synthesized. These units can wire enzymes with nanostructured CNT electrodes through electrografting of the redox polymer or by supramolecular π - π interactions⁷⁶.

1.3.2. Kinetics of redox-active polymers

The rate of charge transport across redox-active polymer films is critical for the efficient transduction of the enzymatic reaction. This rate can be characterized by an apparent electron diffusion coefficient (D_{app}), which is estimated using non-turnover voltammetry of enzyme electrodes in the absence of the enzyme substrate⁴⁵. Typically, the charge transport rate is limited by three processes: the intrinsic barrier to electron self-exchange between polymer-bound redox centers, the transport of ions, and the motion of polymer chains (physical displacement)⁴⁵. The D_{app} of redox-active polymers is significantly lower ($10^{-8} - 10^{-9} \text{ cm}^2 \text{ s}^{-1}$) than the typical D_{app} value of diffusional, small mediators ($10^{-5} - 10^{-6} \text{ cm}^2 \text{ s}^{-1}$) as the displacement of redox centers bound to chains is neither rapid nor extensive. The D_{app} stemming from a combination of physical displacement and electron hopping is expressed as⁷⁷:

$$D_{app} = D_{phys} + \frac{k_{ex} C_E \delta^2}{6} \quad (\text{eq. 7})$$

in which D_{phys} is the diffusion coefficient for the physical displacement of the chains or the redox molecules, k_{ex} is the bimolecular rate constant for electron self-exchange, C_E stands for the concentration of redox species, and δ is the center-to-

center distance between the redox centers (electron hopping distance). Eq.7 can be recombined to the following:

$$D_{app} = \frac{k_{ex}(\delta^2 + 3\lambda^2)C_E}{6} \quad (\text{eq. 8})$$

where λ is the maximum distance across which the tethered redox unit can move. Eq. 8 suggests that D_{app} depends on the concentration of redox couple, and thus j_{peak}^{78} . We see that polymers, for which the length of spacers between the polymer backbone and the redox unit is long, promise for a boost in D_{app} . Long tethers can markedly improve the kinetics of the redox polymers, leading to higher power densities when compared to a redox polymer where the mediator has limited freedom of movement⁷⁹. For example, Soukharev et al. showed that by wiring the enzyme's reaction centers to the polymer and adding eight-atom long tethers, D_{app} could be markedly increased. For this polymer, D_{app} increased by 100 fold with an overpotential of -0.07 V as compared to 0.37 V for platinum⁸⁰.

While the charge transport rate limits the current response of redox-active polymers, diffusion-controlled processes affect the efficiency of biocatalysis, particularly for thick polymer layers⁵⁷. To identify the primary limiting process, CV measurements at different scan rates are performed. A linear dependence of the peak current on the scan rate indicates that diffusion of species doesnot limit the electron transfer rate and that the polymer adheres well to the electrode underneath. Eq. 9 and eq. 10 describe the behavior of two types of where the redox process is limited by charge transport and by diffusion, respectively^{49,81}:

$$i_p = \frac{n^2 F^2 \Gamma}{4RT} \nu \quad (\text{eq. 9})$$

where i_p is the peak current, n is the number of electrons, F describes the Faraday constant, Γ stands for the amount of active material adhered on the electrode surface, v represents the scan rate, R is the gas constant, and T is the temperature.

$$i_p = 0.4463nFA\left(\frac{nFD}{RT}\right)^{1/2}C\sqrt{v} \quad (\text{eq.10})$$

where A is the surface area of the working electrode, D stands for the diffusion coefficient of the electroactive species, and C describes the bulk concentration of the electroactive species. Once the CV curves are recorded, the charge associated with redox reactions can be quantified by dividing the area underneath by the scan rate. The charge normalized by the mass of the polymer on the electrode represents the specific capacity of the polymer film⁸².

1.4. Enzymatic Glucose/O₂ BFCs and polymeric electrodes

Glucose and O₂ are ideal fuel source and oxidant, respectively, because they are readily available in all organic tissues and can be continuously replenished in biological fluids by metabolism. In a typical BFC anode, glucose is catalyzed by the biocatalyst, which is the enzyme, glucose oxidase (GOx), or glucose dehydrogenases (GDH) (**Figure 7a**). The enzyme gets reduced during this reaction. The reaction breaks glucose into gluconolactone and releases electrons, which are then scavenged by O₂ or transferred to other electron acceptors at the cathode. As a result, the enzyme cycles back to its natural oxidized form so that it can once more go through its reaction with glucose. Charge flows through the cell as long as glucose and O₂ are supplied, generating electricity from the circuit (**Figure 7a**). The half-reactions that place in a glucose/O₂ BFC based on redox-active polymers at the bioanode and (bio)cathode are given below:

636 Anode: $C_6H_{12}O_6 + 2OH^- \rightarrow C_6H_{12}O_7 + H_2O + 2e^-$

637 Cathode: $O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$

638 Overall: $C_6H_{12}O_6 + \frac{1}{2}O_2 \rightarrow C_6H_{12}O_7$

639 Enzymes are nature's catalysts which undergo oxidoreduction processes
 640 thanks to specific subunits, called redox cofactors (**Figure 7b**)²⁰. GOx is the most
 641 common enzyme used at the bioanode owing to its stability on surfaces (up to 20
 642 days), selectivity to glucose, high regeneration ability, and commercial availability⁴⁸.
 643 The redox cofactor of GOx is Flavin adenine dinucleotide (FAD). This catalytic pocket
 644 is deeply buried inside the enzyme, hence direct electron transfer is not possible if the
 645 enzyme is in its native structure. Since O_2 competes to take GOx's electrons in its
 646 reduced state after the reaction with glucose, the oxidation current decreases
 647 alongside the production of hydrogen peroxide (H_2O_2). Meanwhile, the concentration
 648 of O_2 available to the cathode as an oxidant decreases⁴⁸. Therefore, enzymes that do
 649 not donate electrons to O_2 are an excellent alternative, particularly when the BFC is
 650 controlled by the amount of O_2 in its compartment. GDHs (glucose dehydrogenases)
 651 are oxidoreductases that do not utilize O_2 as the electron acceptor and instead transfer
 652 electrons to other electron acceptors⁸³. GDH can be equipped with redox cofactors
 653 found in living systems other than FAD, such as nicotine adenine dinucleotide (NAD),
 654 nicotine adenine dinucleotide phosphate (NADP), or pyrroloquinoline quinone (PQQ)
 655 (**Figure 7b**)^{72,83}.

656 For glucose/ O_2 BFCs, O_2 is the oxidizer at the cathode. Besides, it is the
 657 scavenger of electrons in the absence of mediators and ET events in the bioanode
 658 (**Figure 7b**). O_2 is present in all organs and tissues, which makes it ideal to use as the
 659 oxidizer. If the BFC design is a closed system, it should be permeable to O_2 . For the
 660 reduction of O_2 at the cathode, enzymes such as laccase (Lac) or bilirubin oxidase

(BOx) from the family of enzymes called multi-cooper oxidases can provide efficient activity with almost no overpotential⁴⁷. Laccases catalyze the four-electron reduction of dioxygen to water coupled with the one-electron oxidation of phenolic substrates⁸⁴. The disadvantage of Lac lies in its optimum pH (between pH 3 and 5), hindering its compatibility with different materials that may not be stable at this pH. BOx, on the other hand, is preferred over Lac when high performance and stability at neutral pH and tolerance towards chloride anions and high temperatures are required⁸⁵.

For most electrodes, the oxidoreductase enzymes do not comply with direct electron transfer with the anode surface. The sole purpose of redox-active polymers (or low molecular weight redox couples) is thus to mediate the electron transfer between the protein and the anode. The redox-active polymers serve as an electron-conducting relay based on self-exchange reactions among their redox species, which are accepting electrons from the reduced enzyme cofactor (**Figure 7c**). The polymer then transports these electrons to the electrode⁸⁶. A counter process happens for the redox-active polymer at the biochathode. The prerequisite is that the redox polymer has a redox potential value close to the one of the enzyme⁵⁷. The inherently soft nature of polymer chains and the tailored hydrophilicity via side chains provide a more biologically relevant, solvated environment to the enzyme. Redox polymers are expected to increase the lifetime of enzymes by creating a favourable microenvironment and interface for enzymes to bind. If the polymer films exhibit a porous architecture and water uptake, they allow for the facile diffusion of reaction species to the electrode surface. As such, redox-active polymers fulfill two essential tasks in an enzymatic BFC: 1) immobilization and/or encapsulation of the enzyme and, 2) mediating the electrons to the underlying conducting substrate, hence facilitating electrical communication between the electrode underneath and the enzyme cofactor.

For establishing electrical contact with enzymes, aside from linear redox polymers, redox polymer hydrogels have been developed. Redox hydrogels are not different than redox-pendant bearing linear polymers in terms of their redox units or backbone as well as the electron conduction mechanism. The redox centers are chemically bound to the polymer backbone, but the chains are crosslinked (**Figure 7d**). The hydrogels constitute a crosslinked, porous, electron-conducting network in which water-soluble molecules can dissolve and freely diffuse. As discussed in Section 1.3.2, it was found that the rate of the self-exchange of electrons is fastest when the redox units are tethered to the network by flexible spacers that are between 8 and 15 atoms long³⁹. As the polymer is cast on an electrode surface, it forms a film that swells substantially in water. The hydration allows for segmental mobility, which in turn increases the frequency of collisions between the redox centers⁸⁹. The denser the crosslinker is, the lower the segmental mobility of redox centers, lowering the rate of self-exchange of electronic charges. Since redox hydrogels can host enzymes, they have a higher possibility to electrically wire the reaction centers of the enzymes to the electrode, irrespective of their spatial orientation.

Moreover, within their 3D network, they can interconnect reaction centers of multiple enzymes, leading to superior current densities compared with enzyme monolayers packed onto electrode surfaces³⁹. Heller and co-workers instigated the first attempts of crosslinking the enzyme in a redox-polymer matrix⁹⁰. Immobilization of enzyme by covalently binding it to crosslinked polymer network provided high enzyme loading and facile transport of fuel/product from/towards the electrodes while enhancing electrode stability⁴⁴. Another example of crosslinking entails the incorporation of photoreactive benzophenone groups into redox polymers⁹¹. The photochemical crosslinking upon irradiation with UV light allowed to form surface-

attached, water-swelling redox hydrogels, and the simple crosslinking chemistry is compatible even with polymers with no specific functionalities. Bunte et al. found that such bioanodes photogenerated from mixed solutions of enzyme and redox polymer yield high catalytic current responses upon the addition of glucose, even in the presence of ambient O_2 ³⁶.

There are various combinations of redox polymer/enzyme electrodes in the literature used either for biosensing or for BFCs. For instance, Mano et al. immobilized BOx inside a crosslinked network of osmium redox copolymer made of polyacrylamide (PAA) and poly (N-vinylimidazole) (PVI)⁹². The polymeric biocathode exhibited a redox potential of +0.34 V vs. Ag/AgCl and reduced O_2 under physiological conditions (pH 7.4, 0.15 M NaCl, 37°C), reaching 5 mA cm⁻² when poised at +0.3 V vs. Ag/AgCl⁹². When selecting redox polymers in combination with enzymes, other than energetic and polarity compatibility, surface charges ought to be considered. The study of Nieh et al. on the interaction of redox polymers (poly(1-vinylimidazole) (PVI[Fe(CN)₅]), PVI[Os(dcbppy)₂Cl] (dcbppy = 4,4'-dicarboxy-2,2'-bipyridine) and PVI[Os(dmebpy)₂Cl] (dmebpy = 4,4'-dimethyl-2,2'-bipyridine) with four H_2O_2 -generating oxidases including glucose oxidase, sarcosine oxidase, choline oxidase (ChOD) and lactate oxidase revealed that electrostatic repulsions and steric hindrance are enhanced with negatively charged polymers, reducing the activity of the oxidases⁹³. A few other examples for redox polymers at bioanodes or cathodes are listed in **Table 1**.

Table 1. A list of redox-active polymers used as bioanodes and cathodes.

Enzyme	Polymer/ anode	Polymer/ cathode	$J_{\text{oxidation}}$	Environment	Ref
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GOx	PVI/[Os(bpy)Cl]/PEGDGE		400 mA cm ⁻²	0.1 M NaCl buffered with 20 mM phosphate, pH = 7.2, 20 °C	58
Lac	-	[Ru(bipyridine) ₂ (PVl) ₁₀ Cl Cl	240 μA cm ⁻² at 0.63 V vs. Ag/AgCl)	0.05 M phosphate buffer, pH = 5, 20°C	11
Lac	-	Trametes hirsute/Lac/Os-BMCO/GCE	200 μA cm ⁻² at 0.6 V vs. Ag AgCl	0.1 M phosphate /citrate buffer, pH = 4.0, (Ar, air and O ₂), 20°C	94
GOx	MgO-carbon/ poly(vinyl pyridine) + Os(1,1'-dimethyl-2,2'-biimidazole) ₂ -2-[6-methylpyrid-2-yl]imidazole) ^{2+/3+}	-	50 mA cm ⁻² at 0.3 V vs. Ag AgCl	0.1 M PBS, 0.5 M glucose, pH = 7, 37°C	95
FADGDH	F/Os/MgOC/GC (pore size > 100 nm; (1 mg cm ⁻² hydrogel loading)	-	100 mA cm ⁻²	1 M PBS, 0.5 M glucose, pH = 7, 25°C	96
FADGDH	FAD-GDH/GC/poly(1-vinylimidazole)-tethered Os(2,2'-bipyridine) ₂ Cl	-	2.6 mA cm ⁻² at 0.35 V vs. Ag AgCl	25 °C, 0.1 M PBS, 0.2 M glucose, pH = 7, 25°C	97
CDH	CtCDH/CNT/Os-poly(vinylpyridine)-[Os-(N,N'-methylated-2,2'-biimidazole) ₃] ^{2+/3+}	-	0.55 mA cm ⁻² at 0.15 V vs. SHE	50 mM PBS, 50 mM glucose, pH = 7.4	98
FADGDH	FADGDH or GOx/PEGDGE /MWCNT/Os A = 0.0707 cm ²	-	4.2 mA cm ⁻² at 0.12 V vs. Ag/AgCl	0.05 M PBS, pH = 7.4 0.15 M NaCl, 37°C	99

*Abbreviations are given at the end of the document.

In the following sections, we will review the fabrication and performance of state-of-the-art glucose/O₂ biofuel cells that consist of redox-active polymers. We categorize these devices in two classes, those containing polymeric electrodes with a conjugated backbone and those bearing polymers with a redox-active unit, either pendant or integrated to the backbone. The latter group has a large bandgap due to

the absence of π – π conjugation but redox activity inherent to the small molecules attached to them.

1.4.1. Redox-active group bearing polymers in enzymatic glucose/O₂ BFCs

Os-based redox polymers have proved to be up-and-coming candidates integrated both at the cathode and anode of glucose/O₂ BFCs^{57,100}. Corresponding enzymes were mixed with these redox polymers, typically in addition to a crosslinker such as poly(ethylene glycol) diglycidyl ether (PEGDGE). Bioelectrodes were built by simply casting the enzyme-polymer solution onto conducting substrates or making bilayer type architectures. Heller and co-workers explored the use of Os bearing redox polymers to construct biocatalytic electrodes, setting the state-of-the-art polymeric BFCs^{4,80,101,102}. Redox polymers have later been incorporated in self-powered and implantable BFC configurations. The first attempt of an implantable BFC with enzymatic catalysts was in 2001, where Katz et al. presented a BFC acting as a self-powered implantable biosensor. The device gave a 1 μ W power output and was based on BOx and GOx immobilized Os based complexes that made electrical connections to graphite fibers¹⁰³.

A particular advantage of Os comprising redox polymers is their versatile chemistry. Coupling of Os complexes, which contain amine functional groups to epoxy-functionalized polymers with different compositions, has provided a new library of redox polymers with various redox potentials and physicochemical properties¹⁰⁰. There are numerous protocols developed to assemble electrodes based on these polymers. Examples include a cross-linking technique taking advantage of the labile Cl[–], substituted by the amino acid groups of the enzyme¹⁰⁴.

Examples of two redox polymers based on the co-ordination of Os complexes to vinylpyridine or vinylimidazole polymers are illustrated in **Figure 8a** and **b**, respectively⁴⁶. These polymers could efficiently mediate glucose oxidation with co-immobilized GOx. The redox potential of Os^{2+/3+} can be tuned via ligand exchange reactions and/or the introduction of functional groups on the bipyridyl ligands¹³. For example, when functionalized with GOx, the Os polymers where the 2,2'-bipyridine ligands of Os (where X represents –H in **Figure 8a** and **b**) were replaced with 4,4'-diamino-2,2'-bipyridine (where X represents –NH₂ in (**Figure 8a** and **b**) yielded glucose oxidation currents as early as at ~–0.1 V vs. Ag/AgCl¹⁰⁵. Using a crosslinked network of GOx with poly(N-vinyl imidazole[Os(4,4'-dimethyl-2,2'-bipyridine)₂Cl]⁺²⁺-co-acrylimide), Chen et al. built a BFC with a power density of 64 μW cm^{–2} at 23 °C, while the performance increased with elevated temperatures⁵⁹.

Besides GOX, GDH was used as an enzyme incorporated with Os based redox polymers. At the cathode side, Os polypyridine hydrogels have been effective when coupled with BOx, showcasing the use of the redox-polymers with anodic as well as cathodic components. The glucose/O₂ biofuel cell made from Os^{2+/3+}polymers at both electrodes gave a power output of 58 μW cm^{–2} ¹⁰⁶. Another demonstration is that of Cadet et al., who developed a hydrogel incorporated BFC that functions as a self-powered sensor detecting glucose in blood¹⁰⁷. The anode was prepared by depositing a PEGDGE (Poly(ethylene glycol) diglycidyl ether) based hydrogel on carbon fibers, which comprises the redox polymer PVP-[Os(1,1'-dimethyl-2,2'-bisimidazole)₂–2-(6-methylpyridin-2yl)imidazole]^{2+/3+} and the enzyme GDH. The cathode consisted of the same hydrogel network, this time comprising PAA-PVI-[Os(4,4'-dichloro-2,2'-bipyridine)₂Cl]⁺²⁺ and BOx. The two polycationic Os redox polymers made electrostatic complexes with the anionic enzymes, suggesting their stability inside the hydrogel. The polymers had formal

potentials matching to those of the enzymes, ensuring efficient electron transfer. The BFC exhibited an OCV of 0.65 V, and reached an MPD of $129 \mu\text{W cm}^{-2}$ at 0.38 V vs. Ag/AgCl with ca. 8 mM of glucose. Since the device generated a power density scaling with glucose content in human blood, it was employed as a sensor. The authors showed that the loss in power density over time is mainly due to the delamination of the polymer from the electrode surface, whereas biofouling (20%) and inhibition of the enzymes played minor roles. BFC anodes are realized by using anodic enzymes other than GOx and GDH. Some of these involve cellobiose and fructose dehydrogenase (CDH). CDHs are particularly stable enzymes, and similar to GDH, they suppress O_2 conversion in favor of other electron acceptors and catalytically active in a broad range of pHs⁸⁴. Cellobiose dehydrogenase with an $\text{Os}^{2+/3+}$ polypyridine hydrogel yielded a power output of $157 \mu\text{W cm}^{-2}$ by using a platinum black at the cathode¹⁰⁸. Another work reported the synthesis of a pH-dependent, two-electron transfer redox polymer based on a methacrylate backbone bearing covalently bound toluidine blue units and its complex with cellobiose dehydrogenase¹⁰⁹. This polymeric bioanode led to a maximum current density of $60 \mu\text{A cm}^{-2}$ at -150 mV . When wired together with a BOx biocathode, the BFC gave an OCV of 0.72 V and a power density of $6.1 \mu\text{W cm}^{-2}$ ¹⁰⁹.

Other than BOx, Lac is another widely used enzyme at the cathodes of polymeric BFCs owing to its higher redox potential despite its pH-dependent activity¹¹⁰. The redox potential of the Os complex was tuned to match that of the Lac and efficiently reduce O_2 . For instance, a Lac-entrapped modified Os-based hydrogel, namely, poly $[\text{Os}(2,2'\text{-bipyridine})_2(\text{PVI})_{10}\text{Cl}]^+$, led to large current densities when biased even at low potentials (ca. 0.2 V vs. Ag/AgCl) on glassy carbon electrode¹¹¹. An all Os redox polymer comprising GOx and Lac as the corresponding electrodes yielded a maximum power density of $16 \mu\text{W cm}^{-2}$ and an OCV of 0.25 V at pH 7.4¹¹².

In another case, the $\text{Os}^{2+/3+}$ center was tethered to a (2-pyridyl)imidazole based polymer leading to a redox potential (0.72 V vs. NHE) close to the potential of the Lac¹¹³ (0.78 V vs. NHE at pH 6.5). Shen et al. generated a crosslinked network of Os (4,4'-dicarboxylic acid-2,2'-bipyridine) redox units and Lac onto carbon electrodes¹¹⁴. The team found a spontaneous crosslinking reaction that involves the exchange of the inner-sphere Cl^- of the Os (4,4'-dicarboxylic acid-2,2'-bipyridine) complex tethered to partially quaternized poly(4-vinylpyridine) (PVP) by a pyridine ligand of a second PVP chain. The reported composite electrode could catalyze O_2 electroreduction at 0.58 V (vs. Ag/AgCl), indicating effective ET.

Another strategy exploiting the electron mediating of redox-active polymers entails the integration of nanomaterials and metallic NPs that can wire the enzyme active site more effectively to the electrode surface. These nanomaterials improved the surface/volume ratio of electrodes, allowing for the retention of redox polymer and enzyme in the film⁹⁹. For instance, Conghaile et al. coupled deglycosylated pyranose dehydrogenase (PDH) as an enzyme catalyst with multi-walled carbon nanotubes (MWCNTs) alongside an Os redox polymer $[\text{Os}(4,4'\text{-dimethoxy-2,2'-bipyridine})_2(\text{poly}(\text{vinylimidazole}))_{10}\text{Cl}]^+$ (**Figure 8c**)¹¹⁵. The system was crosslinked using glutaraldehyde. Incorporation of MWCNTs with the redox polymer-mediated bioelectrode surfaces caused an increase in the electrode surface area available for enzyme coupling, and in turn, the catalytic current densities⁷². The bioanode was coupled with a biocathode made of BOx, and gold (Au) NPs immobilized on an Au electrode. The resulting BFC gave a maximum power density of 73 and 6 $\mu\text{W cm}^{-2}$ in 5 mM glucose in human blood and saliva, respectively¹¹⁵. In another work, co-immobilized MWCNTs, $[\text{Os}(2,2'\text{-bipyridine})_2(\text{PVI})_{10}\text{Cl}]^+$, and GOx on glassy carbon electrodes resulted in a glucose oxidation current density of 5 mA cm^{-2} (100 mM of glucose at 0.35

838 V vs. Ag/AgCl)¹¹⁸. Current retention of 77% was attained after 24 hours of continuous
839 amperometric testing at 37°C, pH 7.4 buffered solution containing 100 mM of glucose.
840 Other examples include amine-functionalized graphite electrodes modified with
841 crosslinked films of GOx and [Os(4,4'-dimethoxy-2,2'-bipyridine)₂(PVI)₁₀Cl]⁺. The
842 covalently anchored system led to a significant increase in glucose oxidation current
843 density compared to glassy carbon and compared to bare graphite electrodes, the graphite
844 which covalently immobilized the redox polymer had 70% of power retained after 24 h of
845 operation¹¹⁹. A novel patch-type BFC device was designed and reported by Escalona-
846 Villalpando et al.¹²⁰, who immobilized lactate oxidase and the redox polymer
847 dimethylferrocene with linear polyethyleneimine at the anode. The cathode consisted
848 of a mixture of BOx with anthracene modified MWCNTs. Despite not being a glucose-
849 based BFC, this wearable BFC produced an OCV of 0.55 V and a short circuit current
850 of 140 $\mu\text{A cm}^{-2}$, paving the way for new generation wearable-type BFCs. Haddad et
851 al. built a fully polymeric BFC comprising CNT-modified and HNO₃ treated carbon
852 cloths that are coated with Os-complex modified redox polymers entrapping Lac or
853 cellobiose dehydrogenase¹²¹. An MPD of 5.87 mW cm^{-2} was achieved, 125 times
854 higher than in the case of the untreated carbon cloth due to the highly porous network
855 with an increased surface area. Tsujimura et al. reported a mesoporous carbon
856 electrode coated with a hydrogel based on poly(1-vinylimidazole) complex of
857 [Os(bpy)₂Cl] (PVI-Os(bpy)₂Cl). They used a deglycosylated FAD-dependent GDH (d-
858 FAD-GDH) as the biocatalyst¹²². The glucose oxidation current was as high as 100
859 mA cm^{-2} at 25 °C and pH 7 due to efficient enzyme loading in the mesopores, a value
860 30 times higher than flat carbon electrodes functionalized with the same hydrogel.
861 After a 220-day storage test at 4°C, almost all of the initial catalytic current remained
862 and 80% of it was conserved after seven days of continuous operation at 25°C.

Other than Os containing redox polymers, Fc bearing redox polymers have been widely reported^{123–126} as they possess properties such as low cost and reversibility of Fc and its favorable interactions with GOx despite its relatively high redox potentials^{72,127}. A prime example discusses the modification of GOx with a Fc comprising redox polymer, namely, poly(*N*-(3-dimethyl(ferrocenyl)methylammonium bromide)propyl acrylamide) (pFcAc) (**Figure 8d**). The polymer was grown on the GOx surface using atom transfer radical polymerization¹¹⁶. The BFC comprising GOX-pFcAc bioanodes exhibited over an order of magnitude increase in current output and a four-fold increase in MPD ($\approx 1.7 \mu\text{W cm}^{-2}$) compared to the BFC comprising GOx that was physically adsorbed on electrospun polyacrylonitrile fibers integrated with Au NPs and MWCNTs¹²⁸. More recently, GOx and BOx were physically immobilized onto the poly(methyl methacrylate-co-vinylferrocene) modified electrodes¹²⁹. A power density of $323 \mu\text{W cm}^{-2}$, a value claimed to be higher than other Fc-based fuel cells, was attained with 10 mM of glucose at 0.4 V. Another remarkable example is a redox polymer based on 1,1'-dimethylferrocene-modified linear poly(ethylenimine), which was used to build bioanodes that generated currents of up to 2 mA cm^{-2} at 0.3 V versus SCE¹³⁰. The BFC made thereof produced power densities of the order of $146 \mu\text{W cm}^{-2}$ ¹³⁰.

Regarding organic redox-active molecules, naphthoquinone (NQ) derivatives are alternative redox mediators to Os and Fc-based redox polymer hydrogels, promising for increased power densities due to their low redox potentials^{131,132}. Minter et al. synthesized low redox potential NQ units that are modified with epoxy units to covalently modify the host polymer (linear polyethyleneimine, LPEI) and GDH directly (**Figure 8e**)¹¹⁷. The redox potential of the anode could be controlled, ensuring a high OCV (ca. 0.85 V). Binding the enzyme directly to the redox sites enabled a high power of ca. 2.3 mW cm^{-1} at 0.55 V and

100 mM of glucose as the anode was connected to a BOx-based MWCNT cathode¹¹⁷. In another study, GOx and quinone derivatives (p-benzoquinone, naphthoquinone, anthraquinone, and 1,5-Dihydroxyanthraquinone) were co-embedded in PEI which was then immobilized on CNT substrates¹³³. The presence of the two benzene rings of NQ attracted electrons, in turn increasing the catalytic activity for glucose oxidation as corroborated from the high electron transfer rate constant of 1.1 s^{-1} . The BFC produced a high power density ($57.4 \text{ } \mu\text{W cm}^{-2}$) and OCV (0.64 V)¹³³. Hou et al. reported a hydrogel bioanode based on a branched PEI comprising a 1,4-naphthoquinone derivative modified at its electron-withdrawing nitro-group¹³⁴. This modification adjusted the formal potential of the NQ towards more positive values, and the bioanode was completed upon crosslinking the polymer into a hydrogel with the addition of FAD-dependent GDH. When this hydrogel bioanode was combined with a BOx based biocathode, the single-compartment glucose/ O_2 BFC produced a power output of 0.28 mW cm^{-2} and an OCV of 0.69 V .

1.4.2. Conjugated polymer-based enzymatic glucose/ O_2 BFCs

Conjugated polymers (mostly in their doped form) have been employed in enzymatic BFCs due to their reduction-oxidation behaviour in aqueous media, intrinsic conductivity, and softness of their chains. The latter is envisaged to reduce the mechanical mismatch between the rigid, conducting electrode underneath and the soft enzyme. Together with the possibility to endow the chains with different functional groups, these properties make the materials attractive for BFCs. The variability in processing methods compatible with conjugated polymers has allowed easy integration of enzymes and small redox-active compounds and enabled different form factors for the electrodes fabricated. Due to their more extensive abundance and water stability, p-type polymers are mostly used in BFCs. Owing to their positive redox

potentials, they are frequently integrated at the cathode. For instance, polypyrrole (Ppy) was doped with anionic redox-active compounds such as 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) (ABTS) during its electropolymerization on conducting substrates¹³⁵. ABTS displays reversible electrochemistry and compatible formal potential (0.62 V vs. SHE) compatible with Lac and BOx, ideal for use in biocathodes¹³⁶. Ppy was electropolymerized in the presence of Lac and ABTS to form a polymeric biocathode for O₂ reduction, yielding current densities of 3 mA cm⁻² at pH 4¹³⁷.

In the presence of suitable redox mediators, p-type conducting polymers can also be used at the anode. Zebda et al. have synthesized two-layered double hydroxides, Zn₂Cr-ABTS, and Zn₂Al-Fe(CN)₆ and entrapped the redox mediators alongside the corresponding enzymes inside electropolymerized Ppy films deposited on porous tubular electrodes¹³⁸. Entrapping enzymes in the polymer matrix retained better the enzymes than simple adsorption of the surface and increased their lifetime¹³⁹. Lac combined with Zn₂Cr-ABTS cathodic electrode permitted the reduction of O₂, whereas the anodic electrode GOx/Zn₂Al-Fe^{III}(CN)₆ was used for the oxidation of glucose. With a two-compartment configuration comprising these Ppy electrodes, the BFC exhibited an MPD of 45 μW cm⁻² at 0.2 V. Crepaldi et al. fabricated bioanodes based on polyamidoamine dendrimers that immobilized GOx¹⁴⁰. The bioanode further contained ferrocenium hexafluorophosphate (FHFP), entrapped in electropolymerized Ppy films. The Ppy material led to an MPD of ca. 130 μW cm⁻² at pH 5.0 with 100 mM of glucose¹⁴⁰.

A variety of redox mediators such as porphyrin, Fc, Os, and ruthenium complexes have been entrapped in electropolymerized Ppy, and some are acting as functional dopants^{141–145}. Ppy films comprising FHFP and PQQ promoted ET between

GOx and the carbon electrode underneath¹⁴⁶. Ppy combined with bis-(bipyridine)-(5-amino-phenanthroline) ruthenium bis (hexafluorophosphate) and 4,4-sulfonyldiphenol allowed for ET events at the Lac biocathode¹⁴⁶. When the electropolymerization was performed in ultrapure water, thicker Ppy films with high conductance could be made¹⁴⁶. The BFC made of these films showed an MPD of $3.1 \mu\text{W} \cdot \text{mm}^{-2}$ at 0.28 V in PBS (pH 7.4). In human serum, the same cell generated $1.6 \mu\text{W} \cdot \text{mm}^{-2}$ at 0.21 V, despite losing ~11% of its power density each day during a three-day continuous operation¹⁴⁶. Cardoso et al. prepared Lac-based biocathodes containing different redox mediator species, namely porphyrin, Fc, Os, and Ru complexes, all entrapped in an electropolymerized Ppy matrix that is immobilized on carbon-based platforms¹⁴⁰. Methanol/O₂ BFCs reached MPD values of 81 and 71 $\mu\text{W} \cdot \text{cm}^{-2}$ for the [Ru(bpy)₂Cl₂] and the [Os(bpy)₂Cl₂] complexes at pH 4.5, respectively.

PPy based BFC electrodes have been modified with other high-performance carbon nanomaterials. For instance, MWCNT electrodes were functionalized through the electropolymerization of pyrrole monomers that contain pyrene or *N*-hydroxysuccinimide groups¹⁴⁷. These groups immobilized Lac via chemical grafting or non-covalent binding and resulted in high O₂ reduction currents ($1.85 \text{ mA} \cdot \text{cm}^{-2}$) and enzyme stability (50% after one month)¹⁴⁷. Thanks to the ease of chemical modification of the monomer, enzymes can be covalently bound to the conjugated polymer instead of physical entrapment, preventing their leaching and ensuring more stable systems. Merle et al. built bioelectrodes where GOx and Lac were covalently grafted onto a poly(aminopropylpyrrole), which was then electropolymerized onto an electrode surface¹⁴⁸. The amino groups of the conjugated polymer film reacted with the enzymes, and the flexible alkyl spacer used between the components preserved the enzymatic activity against the denaturation of enzymes. Two redox mediators

(HQS and ABTS, at anode and cathode, respectively) were immobilized in a hydrogel network cast on top of these enzyme-polymer electrodes. The MPD of the resulting BFC was ca. $20 \mu\text{W cm}^{-2}$ with 10 mM glucose in PBS (pH 7.4), and remained constant after intermitted use over 45 days.

Another strategy entailed the use of Ppy as a conducting encapsulation layer. Habrioux et al. coated enzymes (BOx and GOx) and mediators (ABTS and HQS) on two carbon tubes, which were encapsulated and separated by an electropolymerized Ppy film (**Figure 9a**)¹⁴⁹. The Ppy film separated the anode and cathode in a tubular, concentric configuration, and dissolved O_2 was supplied to the cathode separately from the electrolyte. In this configuration, O_2 circulating through the inside of the cathode tube diffused to the external surface of the tube to react with the immobilized BOx¹⁴⁹. This BFC generated an MPD of ca. $42 \mu\text{W cm}^{-2}$ at 0.3 V in PBS with 10 mM of glucose¹⁴⁹. Ppy is also compatible with the layer-by-layer deposition technique to fabricate enzymatic bioanodes¹⁵⁰. A bioanode was fabricated on a glassy carbon electrode that comprised Ppy, silver NPs, graphene oxide as the electroactive part and horse spleen ferritin protein, and GOx as the catalysts deposited in a layer-by-layer fashion¹⁵¹. The electrode yielded a current response of 5.7 mA cm^{-2} ¹⁵¹.

Thiophene based polymers have been also used in bioelectrocatalysis. For instance, the O_2 insensitive enzyme, pyrroloquinoline quinone dependent glucose dehydrogenase (PQQ-GDH) was covalently bound to a PT copolymer electropolymerized on MWCNTs¹⁵² (**Figure 9b**). While the copolymer acted as an immobilization reagent, it allowed for electrochemical wiring of PQQ-GDH and transferred electrons generated upon glucose oxidation to the electrode, indicated by an anodic current reaching high values at 0 V vs. Ag/AgCl¹⁵³. The OCV of this

bioanode in the presence of 5 mM glucose was -0.22 V vs. Ag/AgCl, reflecting the efficient communication between PQQ-GDH and MWCNTs¹⁵³.

In another work comprising PT-based polymers, Lac was physically adsorbed on a copolymer containing 3-methylthiophene and thiophene-3-acetic acid, generating a conducting polymer biocathode that gave a large O_2 reduction current (i.e., $87 \mu A cm^{-2}$)¹⁵⁵. The same copolymer was used in a BFC comprising the GOx/copolymer at the anode and the BOx/copolymer at the cathode yielding an MPD of $0.15 mW cm^{-2}$ at $0.35 V$ ¹⁵⁶. A PQQ-GDH modified thiophene copolymer film electropolymerized on a Buckypaper composed of compressed MWCNTs was coupled to a (BOx)-MWCNT-based biocathode in a membrane-free configuration (**Figure 9c**)¹⁵⁴. The PQQ-GDH-modified electrode oxidised glucose at potentials more positive than -0.09 mV, and the BOx-modified electrode reduced O_2 at potentials more negative than $+0.51$ mV (**Figure 9c**)¹⁵⁴. A BFC based on these components was built in a small geometry ($2 \times 3 \times 2 mm^3$) and tested in human serum as well as in a living gray garden slug. The BFC power was dependent on glucose and varied between 2-10 μW . In blood, the OCV and power values were lower than those obtained in the buffer (**Figure 9d**). When implanted in the animal which has a typical glucose concentration of ca. 0.7 mM in its hemolymph (blood like biofluid of invertebrates), the OCV was ca. 0.31 mV and MPD was $200 \mu W cm^{-3}$, smaller by a factor of ca. 2.4 compared to buffer conditions¹⁵⁴.

Polyaniline (PANI) is another conducting polymer used in BFCs. PANI nanowires were electrochemically grown on reduced graphene oxide electrode which, was bound to positive-charged (oxidized) PANI nanowires surface via electrostatic interactions¹⁵⁷. A bioanode was fabricated as fructose dehydrogenase integrated into the PANI construct. When combined with a Lac functionalized PT copolymer film, this

BFC exhibited an OCV of 0.55 V and a power density of 0.36 mW cm^{-2} at a cell voltage of 0.3 V in an O_2 -saturated acetate buffer solution (0.05 M, pH = 4.5) with 0.2 M of fructose¹⁵⁸. Besides, PANI has been reported to electrocatalytically reduce dissolved O_2 in acidic conditions, which makes it a promising cathode material¹⁵⁹.

A similar property is identified for EDOT derivatives, most effective when the polymer is in the reduced (undoped) state. Ohayon et al. electropolymerized a copolymer of PEDOT with hydroxyl PEDOT (i.e., p(PEDOT:EDOTOH)) and showed its electrocatalytic activity towards O_2 reduction¹⁶⁰. This polymer film acted as the cathode of a glucose/ O_2 fuel cell. The anode was an n-type semiconducting polymer (NDI-T2) that was functionalized with an adsorbed layer of GOx (**Figure 10a-b**)¹⁶⁰. The polymer film acted as a redox mediator and a semiconductor and had direct communication with the enzyme, which resulted in an increase in its conductivity upon oxidation of glucose. The BFC generated ca. 0.3 V alongside an MPD of $2.8 \mu\text{W cm}^{-2}$ for 10 mM of glucose in PBS (**Figure 10 c**). The bioelectrode could operate in a complex medium such as human saliva and the polymeric BFC was also used as a circuit component (**Figure 10 d-e**). This report is the first demonstration of an enzymatic fuel cell that does not rely on redox mediators while using the conjugated polymers as catalysts¹⁶⁰.

In addition to the experimental work on redox-polymers in BFCs, computational studies have been reported as early as 2009 as a means to complement further and understand these systems. The outcome of these simulation studies highlights the impact of enzyme loading in the catalyst layer, electrode surface area, and hydrogel film thickness on the performance of the BFC^{79,161,162}. **Table 2** below summarizes the performance of the components of selected BFCs that comprise redox-active polymers.

1037 **Table 2.** List of biofuel cells bearing redox-active polymers as electrodes along with
1038 their performance.

Type of BFC	Anode	Cathode	MPD / E_{cell}	Environment	Ref
Membraneless Glucose/O ₂	GOx/PVI - [Os(N,N'-dialkylated -2,2'-bisimidazole)] ^{2+/3+} /PEDGE/CF	Lac/PVI-[Os-2,2',6',2"-terpyridine-4,4'-dimethyl-2,2'-bipyridine) ₂ Cl] ^{2+/3+} /PEDGE/CF	268 $\mu\text{W cm}^{-2}$ / 0.78 V	20 mM PBS, 0.14 M NaCl, pH = 7.4 37.5°C, air	105
Membraneless β -lactose/air	CDH/Os-polymer/Graphite	Lac/Os-polymer cathode/Graphite	1.9 $\mu\text{W cm}^{-2}$ / 0.6 V	100 mM phosphate-citrate buffer, pH = 3.5, 34 mM lactose, air	21
Membraneless Glucose/O ₂	GOx/PVP-[Os(N,N'-alkylated-2,2'-biimidazole) ₃] ^{2+/3+} /CNT fibres	BOD/PAA-PVI-[Os(4,4'-dichloro-2,2'-bipyridine) ₂ Cl] ^{+2/} /CNT fibres	740 $\mu\text{W cm}^{-2}$ / 0.57 V	20 mM PBS, 0.14 M NaCl, pH = 7.2, 15 mM glucose, 37°C	163
Membraneless Glucose/O ₂	"wired" GOx//PEGDGE/CF (diameter = 7 μm , 2 cm long)	Lac/PVI/poly(4-vinylpyridine) [Os(N,N'-dimethyl-2,2'-biimidazole) ₃] ^{2+/3+})/PEDGE	350 $\mu\text{W cm}^{-2}$ / 0.88 V	Stagnant citrate buffer, pH = 5, 15 mM glucose, 37.5°C	80
Membraneless Glucose/O ₂	GOx/[Os(4,4'-dimethoxy-2,2'-bipyridine) ₂ (poly(vinylimidazole)) ₁₀ Cl] or [Os(4,4'-dimethyl-2,2'-bipyridine) ₂ (poly(vinylimidazole)) ₁₀ Cl]/GA/CNT/Graphite	O ₂ reducing BOx/Au NPs/Au	275 $\mu\text{W cm}^{-2}$ at 0.3 V MPD _{human blood} = 73 $\mu\text{W cm}^{-2}$	50 mM PBS, pH = 7.4, 150 mM NaCl, 5 mM glucose, 20°C	115
Membraneless Glucose/O ₂	GOx/[Os(4,4'-dimethoxy-2,2'-bipyridine) ₂ (poly(vinylimidazole)) ₁₀ Cl] ⁺ and [Os(4,4'-dichloro-2,2'-bipyridine) ₂ (poly(vinylimidazole)) ₁₀ Cl] ⁺ /PEGDGE / Graphite	ThLacc or MbOD/PEGDGE / Graphite	43 $\mu\text{W cm}^{-2}$ at 0.25 V, MPD _{retention.} = 70% after 24 h	PBS, pH = 5.5, 0.1 M glucose, 37°C	119
Membraneless (lactate)	LOx/FcMe ₂ -LPEI/EDGE/CNF-Ppy	Lac/An-MWCNT/TBAB-Nafion/CNF-Ppy	71.2 $\mu\text{W cm}^{-2}$ / 0.59 V	0.1 M PBS, pH = 5.7, 40 mM lactate, 37°C	120

Membraneless Glucose/O ₂	GOx/PVP/[Os(N,N'-dialkylated-2,2'-biimidazole) ₃] ^{2+/3+} /PEGDGE/CF	BOx/PAA/PVI/[Os(4,4'-dichloro-2,2'-bipyridine) ₂ Cl] ⁺² /PEGDGE/CF	315 $\mu\text{W cm}^{-2}$ / 0.59 V	20 mM PBS, 0.14 M NaCl, 15 mM glucose, pH = 7.24, 37°C	164
Membraneless Glucose/O ₂	Poly(MMA-co-VFc)/GOx/Au	Poly(MMA-co-VFc)/BOD/Au	323 $\mu\text{W cm}^{-2}$ at 0.4 V	Aerated 100 mM PBS, 10 mM glucose, pH = 7.4, 45°C	129
Membraneless Glucose/O ₂	Poly(TAA-co-MT)/Fc/GOx/ Au	aPoly(TAA-co-MT)/Fc/BOx/Au	1 $\mu\text{W cm}^{-2}$ at 0.56 V	100 mM PBS, pH = 7.4, 10 mM glucose	165
Membraneless Glucose/O ₂	<i>Am</i> PDH/ngDHC _t CDHC _{310Y} /Os/ PEGDGE/ Graphite	<i>Mv</i> BOD/PEGDGE/Graphite	20 $\mu\text{W cm}^{-2}$ / 0.55 V	0.1 M PBS, pH = 7.4, 100 mM glucose, 20-35°C	166
Membraneless Glucose/Air	GDH/azine/hydrogel (MG)/EGDGE/MWCNT	Pt (gas permeable)/Vulcan XC-72/Nafion 212	106 $\mu\text{W cm}^{-2}$ / 0.514 V	Phosphate/nitrate buffer, pH = 7.4	167
Membraneless Glucose/O ₂	GOx/HQS/Ppy (anodic polymerization at 0.9 V vs. Ag AgCl)/Carbon tube	Lac/ABTS ²⁻ /Ppy (anodic polymerization at 0.9 V vs. Ag AgCl)/Carbon tube	27 $\mu\text{W cm}^{-2}$ at 0.25 V	PBS, pH = 5-7, 10 mM glucose, 37 °C, under N ₂	168
Membraneless Glucose/Air	GOD/Fc/Glycerol/Graphite disc/BSA/glutaraldehyde	Lac/ABTS/Glycerol/Graphite/ 0.1 wt% Nafion	23 $\mu\text{W cm}^{-2}$ / 0.63 V	0.1 M PBS, pH = 6, 50 mM glucose, 30 °C	169
Membraneless Fructose/O ₂	FDH/CP	Lac/An-MWCNTs/TBAB-modified Nafion/CP	34.4 $\mu\text{W cm}^{-2}$ / 0.707 V	50 mM citrate, 100 mM fructose, pH = 4.5	170
Glucose/O ₂	[Os(4,4'-diamino-2,2'-bipyridine) ₂ (poly(<i>N</i> -vinylimidazole))-(poly(<i>N</i> -vinylimidazole)) ₉ Cl] ⁺ Cl ⁻ /PEGDGE /Graphite	[Os(phenanthroline) ₂ (poly(<i>N</i> -vinylimidazole)) ₂ -(poly(<i>N</i> -vinylimidazole)) ₈] ⁺ Cl ₂ ⁻ /PEGDGE /Graphite	40 $\mu\text{W cm}^{-2}$ / 0.4 V	0.1 M PBS, pH = 5.5, 10 mM glucose, 0.1 M NaCl, 37 °C	112
Glucose/O ₂	<i>AWrbA</i> /Os redox hydrogel/SWCNT-Graphite/PEGDGE	Pt black	12 $\mu\text{W cm}^{-2}$ / 0.165 V	8 mM NADH in MOPS buffer (0.1 M), pH 7.5, under O ₂	171

Glucose/O ₂	Fc/GO _x ⁻ FADH ₂ /GC (Immobilization through irradiation)	BOD- ABTS ²⁻ /Nafion matrix/FBP	26 $\mu\text{W cm}^{-2}$ at 0.2 V / 0.55 V	Quiescent saturated PBS, pH = 7.2, 5 mM glucose, O ₂ , 37°C	126
Glucose/O ₂	GOx/Nafion 117/TMPD/GC	Lac/[Os(2,2'- bipyridine) ₂ (polyvinylimidaz- ole) ₁₀ Cl] ⁺²⁺ and [Os(4,4'- dichloro-2,2'- bipyridine) ₂ (poly vinylimidazole) ₁₀ Cl] ⁺²⁺ /PEGDGE/ GC	52 mW cm ⁻² at 0.21 V	0.05 M PBS, 0.1 M glucose, 0.15 M NaCl, pH = 7.4, under O ₂ , 37°C	172
Glucose/O ₂	PVP/[Os(1,1'- dimethyl- 2,2'-bisimidazole) ₂ -2-(6- methylpyridin- 2yl)imidazole] ^{2+/3} +/ PEGDGE /GC	PAA/PVI- [Os(4,4'- dichloro-2,2'- bipyridine) ₂ Cl] ⁺² +/ PEGDGE /GC	129 $\mu\text{W cm}^{-2}$ at 0.38 V	8.22 mM glucose in deoxygenated human blood, 37°C	173
Glucose/O ₂	FAD-CrCDH and PQQ- sGDH/Os/EDT/ Graphite	MvBOx/Graphite	3 $\mu\text{W cm}^{-2}$ / 0.54 V	12 mM PBS, pH = 7.4, 0.14 M NaCl, 2.7 mM KCl, 5 mM glucose, 30-37°C	174
Glucose/O ₂	PA/PQQ- GDH/PABSMa/ BP	BOD/PQQ- CNT/EDC-NHS solution/BP	100 $\mu\text{W cm}^{-2}$ / 0.71 V MPD _{saliva} = 88 $\mu\text{W cm}^{-2}$ / 0.665 V	100 mM citrate phosphate buffer, 5 mM glucose, pH = 7	175
Glucose/O ₂	GOx/PANAM/Fc -Ppy/Carbon cloth	Gas diffusion membrane (Pt 20% in Carbon hot- pressed in Nafion NRE-212 membrane)	130 $\mu\text{W cm}^{-2}$ / 0.416 V	PBS, pH = 5 0.1 M glucose, 25°C, air	140
Glucose/O ₂	GC/bi-layer polymer membrane; inner layer: Dp/2-methyl-1,4- naphthoquinone (K ₃)/KB, outer layer: glucose GDH	Polydimethylsilo- xane-coated/Pt	14.5 $\mu\text{W cm}^{-2}$ / 0.62 V	Air-saturated PBS, pH = 7 0.5 mM NADH, 10 mM glucose, 37°C	176

Hydrogen/ Glucose	DvMF-[NiFe] and (DvH- [NiFeSe]) + P(N ₃ MA-BA- GMA)/GOx/Py ₂ Ox or CAT/P(SS- GMA-BA)	Oxidase- HRP/carbon cloth/CMFs/CNT	530 $\mu\text{W cm}^{-2}$ at 0.85 V / 1.15 V	0.1 M phosphate buffer, 3 mM glucose, 20°C	177
Glucose/O ₂	P(GMA-BA- NIPA)-TB poly(methacrylat e)/GOx/ Graphite	MvBOx/Graphite	1.2 $\mu\text{W cm}^{-2}$ / 0.65 V	PBS, pH = 7, 4.8 mM glucose, 20°C, argon	178
Glucose/O ₂	GC/PaoABC/ [Os(bpy) ₂ Cl] ^{+/} /PE GDGE/Esterase	CNT/CMF/Grap hite/BOD/	0.63 $\mu\text{W cm}^{-2}$ / 0.5 V	0.1 M acetate buffer, pH = 4.5, 20°C, cathode chamber under O ₂ , Anode chamber under argon	179
Glucose/O ₂	GOx/PVP- [Os(N,N'- dialkylated-2,2'- bis- imidazole) ₃] ^{2+/3+} / PEGDGE/40- Carb(HIPE)	BOD/40- Carb(HIPE)	205 $\mu\text{W cm}^{-2}$ at 0.4 V	Quiescent, 100 mM PBS, pH = 7.2, 50 mM glucose, 37 °C	180
Glucose/O ₂	GOx/FcMe ₂ -C ₃ - LPEI/GC	Lac/An- MWCNTs/TBAB -modified Nafion	56.8 $\mu\text{W cm}^{-2}$ / 0.819 V	Anodic compartment: 50 mM sodium phosphate, 50 mM NaCl, 60 mM glucose, pH = 7.0. Cathodic compartment : 50 mM citrate, pH = 4.5	170
Glucose/O ₂ Microfluidic BFC (Double-Y- shaped microchannel)	GOx/Fc-C ₆ - LPEI/ EGDGE/PPF	MWCNTs/Lac/T BAB-Nafion/ EGDGE/PPF	64 $\mu\text{W cm}^{-2}$ / 0.54 V at 70 mL min ⁻¹	100 mM glucose, 100 mM PBS, pH = 7.4, 25 °C Catholyte: 150 mM citrate buffer, pH = 4.5	181
NADH/ H ₂ O ₂	PQQ/Au/EDC	MP-11/Au/EDC	$W_{\text{max}} = 8 \mu\text{W}$ / 0.32 V (W_{max} : Maximum electrical power)	0.1 M Tris-HCl buffer, pH = 8.0 Anodic fuel : 0.001 M NADH + 0.02 M CaCl ₂ . Cathodic oxidizer: 0.001 M H ₂ O ₂	182
Implantable Tre/O ₂	Tre/GOx/Os(dm- bpy) ₂ Cl PEGDGE/Carbo n rod	BOD/Os(bpy) ₂ Cl /PEGDGE/Carb on rod	100 $\mu\text{W cm}^{-2}$ at 0.2 V	50 mM Trehalose in PBS, air	183

1.5. Conclusions and Outlook

Redox-active polymers have received a great deal of attention due to their practicality and effectiveness in an array of energy storage devices, including BFCs, where they act as electroactive components coating more conducting substrates. The most appealing property of these materials is the wide range of selection of redox-active units and backbones alongside the ease of processing into various forms. It is possible to change the redox potentials, hence the compatibility with the enzymes selected at the electrodes by changing the chemistry of the redox units, their polarity, and how they are bound to the main chain (length of spacers), all affecting the final properties of the polymer. A new polymer tailored to the desired features can be realized via simple chemical modifications, giving a handle to control electron transfer rates and interaction with enzymes as well as reaction species. BFCs, in general, offer competitive advantages over conventional power sources. These include the utilization of renewable and non-toxic components, high reaction selectivity and activity of the biocatalysts, an abundance of biofuels, and physiological operating conditions (human body temperature and near-neutral pH)¹⁸⁴. Next-generation redox-active polymers will certainly need macromolecular engineering to improve their properties. Adapting the properties of redox polymers for BFCs will allow to immobilize enzyme more effectively, facilitate electron transfer, design new 3D enzyme-electrode interfaces, and protective matrixes, altogether enhancing the power and energy density and, most importantly, the operational stability of the devices. In addition, as the interest in wearable and implantable electronics grows, we will need green power sources coming from the BFCs to power the biosensors and bioactuators. Despite the presence of technical obstacles to overcome, there is a wide range of applications for BFCs. We envision that the next era will see the development of redox-active polymers

that are furnished with extra functionalities. These will include biodegradability, flexibility, and self-healing, which will be as crucial as high power outputs for niche applications. For these wearable and implantable device configurations, next-generation redox-active polymers must endorse patterning in small dimensions, where direct electron transfer and effective enzyme immobilization will be needed more than ever.

Abbreviations:

An: Anthracene; AmPDH: Pyranose dehydrogenase from *Agaricus meleagris*; ABTS: 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonate) diammonium salt; BOD: Bilirubin oxidase; BMCO: Blue multicopper oxidases; BP: Bucky paper; BSA: Bovin serum albumin; CDH: Cellobiose dehydrogenase; CtCDH: *Corynascus thermophiles* cellobiose dehydrogenase; CNF: Carbon nanofiber; CMFs: Carbon microfibers; CAT: Catalase; DvMF: *Desulfovibrio vulgaris* Miyazaki F; DvH: *Desulfovibrio vulgaris* Hildenborough; Dp: Diaphorase; DH_{CtCDH}: *Corynascus thermophilus* cellobiose dehydrogenase; EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; EDT: 2,2'-(ethylenedioxy)diethanethiol; EGDGE: Ethylene glycol diglycidyl ether; FAD-CtCDH: Lavodehydrogenase domain of cellobiose dehydrogenase from *Corynascus thermophiles*; FADGDH: Flavin adenine dinucleotide-dependent glucose dehydrogenase; fBP: Functionalized buckypaper; FDH: Fructose dehydrogenase; GDH: Glucose dehydrogenase; GCE: Glassy carbon electrode; GA: Glutaraldehyde; HQS: Hydroxyquinolinone-5-sulfonic acid hydrate; HRP: Horseradish peroxidase; KB: Ketjen black; LOx: Lactate oxidase; Lac: Laccase; MPD: Maximum power density; mp: microperoxidase; MvBOx: Bilirubin oxidase from *Myrothecium verrucaria*; MG: Methylene green; MvBOd: *Myrothecium verrucaria* bilirubin oxidase; MgOC: MgO-templated carbon; MP-11: Microperoxidase-11; NADH: 1,4-dihydronicotinamide adenine dinucleotide; NHS: N-hydroxysuccinimide; SHE: Standard hydrogen electrode; ORR: Oxygen reduction reaction; Os(dmobpy)₂PVI: [Os(4,4'-dimethoxy-2,2'-bipyridine)₂(polyvinyl imidazole)₁₀Cl]Cl; PEGDGE: Polyethylene glycol diglycidyl ether; PVI: Poly(vinylimidazole); PQQ: Pyrroloquinoline quinone; PQQ-sGDH: Apo-enzyme of PQQ-dependent soluble glucose dehydrogenase; Ppy: Polypyrrole; P(N₃MA-BA-GMA): (Poly(3-azido-propyl methacrylate-co-butyl acrylate-co-glycidyl methacrylate)-viologen; Py₂Ox: Pyranose oxidase; P(SS-GMA-BA): Poly(4-styrene sulfonate-co-glycidyl methacrylate-co-butyl acrylate); PQQ-GDH: Pyrroloquinoline quinone dependent glucose dehydrogenase; PANAM: Polyamidoamine; PAA: Poluanionic poly(acrylic acid); P(GMA-BA-NIPA): Poly(glycidyl methacrylate-co-butyl acrylate-co-N-isopropylacrylamide); poly(MMA-co-VFc: Poly(methyl methacrylate-co-vinylferrocene); Poly(TAA-co-MT): Poly(3-thiopheneacetic acid-co-3-methylthiophene); PaoABC: Aldehyde oxidoreductase isolated from *Escherichia coli*; PG: Pyrolytic graphite; PBS: Phosphate saline buffer; PABMSA: Poly(3-aminobenzoic acid-co-2-methoxyaniline-5-sulfonic acid); PPF: Pyrolyzed photoresist film; WrbA:

Tryptophan (W) repressor-binding proteins from *Escherichia coli* (EcWrbA) and *Archaeoglobus fulgidus* (AfWrbA); Tre: Trehalase; ThLacc: *Trametes hirsuta* laccase; TB: Toluidine Blue; Tr: Disaccharide trehalose; TMPD: N,N,N',N'-tetramethyl-p-phenylenediamine; TBAB: Tetrabutylammonium bromide.

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