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Research review paper

# Bioelectrocatalytic systems for health applications

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ABSTRACT

We present a brief overview of bioelectrocatalytic devices for *in vitro* health applications, including food safety and environmental analysis, focusing on microelectrode- and microfluidic-based biosensors, paper-based point-of-care devices and wearable biosensors. The main hurdles and future perspectives are discussed. We then consider the role of electron transfer between a biocatalyst and an electrode in biosensor design. Brief descriptions of indirect, direct and mediated mechanisms are given. The principal strategies, as well as recent developments for modulation of electron transfer in biocatalytic systems are summarised. In conclusion, we highlight some of the challenges associated with improving these redox systems.

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## 1. Introduction

Bioelectrocatalytic systems are based on biological entities which catalyse electrochemical processes that concern the interaction between chemical change and electrical energy. Biocatalytic devices incorporate either enzymes, whole cells, parts of cells or tissues as a catalytic element. Such systems can be used for various purposes, such as power generation, bioremediation, chemical synthesis and biosensing. In this review, we focus on biosensing applications of biocatalytic systems in health monitoring, food safety and environmental analysis and mention the application of biocatalytic systems as power supplies for biosensing devices. In biosensors, the biocatalyst is the biorecognition element that recognises the target analyte by chemical interaction and transforms this information into an electrically detectable signal.

Although various biorecognition elements have been used for biosensor construction, enzymes are the oldest (Clark and Lyons, 1962) and still most commonly used biorecognition element in biosensing. Of particular interest for electrochemical biosensing is one specific class of enzymes, the oxidoreductases, which catalyse oxidation–reduction reactions along with the subclass, oxidases, which catalyse redox reactions involving molecular oxygen as the electron acceptor. Enzymes are characterised by high turnover rates and high, often specific, selectivity for a desired analyte. These properties, together with the simplicity of enzymatic biorecognition and their relatively low cost, make enzymatic bioelectrocatalytic systems almost indispensable for analysis in complex matrixes, such as biological fluids and environmental samples. Hence, they are extremely important in health applications. Given the prevalence of diabetes and the excellent catalytic properties of glucose oxidising enzymes, it is not surprising that blood glucose biosensors comprise around 85% of the word market for biosensors (Turner, 2013). Enzymes, however, also have several disadvantages, such as complex production and purification processes, limited lifetime and difficulties in multianalyte analysis due to the high enzyme specificity.

Microbial cells represent an alternative biocatalyst for biosensing. The catalysis in this case is implemented by enzymes contained within the cell. Whole–cell bioelectrocatalysis was first reported in 1911 (Potter, 1911), but it was applied for biosensing only by Divies in 1975. This biosensor was based on the use of *Acetobacter xylinum* with an oxygen electrode. The development of microbial biosensors represents a logical extension of the enzyme electrode concept, since the signal generation is analogous to those systems and is based on enzymatic biocatalytic reactions. In essence, biocatalytic systems using microbial cells, part of cells or tissues, can be considered as a 'bag of enzymes' (Ikeda et al., 1996). Use of whole cells can overcome some of the above mentioned disadvantages associated with enzymatic bioelectrocatalysis. Application of whole cells does not require enzyme purification, supports better stability of biocatalytic systems and permits sensing of multiple analytes using a single biocatalytic element. However, such systems also suffer from a number of limitations compared to enzymes, such as the requirement for nutrient and energy supplies to support living cells, slower rates of signal generation and lack of specificity. The last point can be regarded both as an advantage and a disadvantage of microbial biocatalysis, depending on the nature of the application. For example, use of whole cells is advantageous when a class of analytes needs to be monitored, such as marine toxins (Wang et al., 2015) or heavy metals (Chouteau et al., 2005). For detection of individual analytes, such as glucose (Noiphung et al., 2013) or lactate (Kim et al., 2014) in complex matrices, application of enzymes is undoubtedly more effective.

Bioelectroatalytic systems are dependent on electrochemical contact between the biocatalyst and an electrode. Enzymatic bioelectrocatalysis is possible indirectly via electroactive intermediates in the reaction, via direct electron transfer (DET) between the active site of the biocatalyst and the electrode, or via mediated electron transfer (MET), where small molecules that are artificially introduced into the system, shuttle electrons between the enzyme and the electrode. Whole cells establish electron transfer with electrodes using similar mechanisms. DET is accomplished via cytochromes located in the cell outer membrane (Lovley, 2008) or by specific biological nanostructures (Reguera et al., 2005). Biosynthetic redox mediators, such as flavins, phenazines and quiones (Freguia et al., 2012) or chemical exogenous mediators (Schröder, 2007) are used for MET. Due to the direct influence of the electrochemical contact between the biological and physical parts of the sensor on its analytical performance, this issue should be given special attention when designing new biocatalytic systems for biosensing applications. Therefore, in the second part of this review, we will summarise some well-known methodologies to create efficient electron transfer in biocatalytic systems as well as the key recent findings in this area, focusing mainly on examples of enzymatic bioelectrocatalysis.

### *1.1. Biosensors for health applications*

Biosensors have achieved considerable success in both the commercial (US$ 13 billion annual turnover) and academic arenas and the need for new, easy-to-use, home and decentralised diagnostics is now greater than ever. It is rapidly becoming apparent that such sensors can contribute substantially to reducing healthcare costs and to enhancing the quality of life for our citizens. Healthcare spending is growing unsustainably and according to the WHO, has already exceeded 18% of GDP in the USA and 9.5% of GDP in Europe. Maintaining a healthy and sustainable environment is also top of the political agenda and food safety and personal security are key concerns. New thinking is crucial to finding effective solutions that deliver the high quality of life rightly demanded by our ever ageing population while leveraging technology to deliver this in a cost-effective manner. Several key drivers are coming together to form a "perfect storm" that may just finally catalyse change to our 2500 year-old model of healthcare delivery and health maintenance. Personalised medicine recognises that every individual is different and needs a tailor-made health package; these differences can only be identified with an appropriate suite of diagnostics. Individuals are increasingly recognising that data about their bodies should be owned by them and that they should have the choice to use and supplement this information. This generates consumer choice and drives evidence-based payment, where regimens and treatments are paid for on the basis of successful outcomes, which consequently need to be measured. Focus on the individual and their needs drives decentralisation and the possible radical restructuring of how we deliver health management both nationally and internationally. We already see "health rooms" in pharmacies, but the next step will be health rooms in your home, in your pocket or on your wrist. These advances are underpinned by technologies facilitating mobility and data processing. At the core of all this, however, is rapid, convenient and easy ways to measure our body chemistries at the genomic, proteomic and metabolomic levels and the body's associated interaction with the environment and the food we eat. Next generation diagnostics fabrication is targeting fully-integrated platforms such as the all-printed biosensing systems, integrated sampling and wearable devices. Further development will result in cost reduction and a diversity of formats such as point-of-care tests, smart packaging, telemetric strips and print-on-demand analytical devices. Realisation of these paradigm-changing scenarios requires new business models, the effective harnessing of emerging technology, inspired vision from clinical partners or other "users", and leading-edge engineering and design, to produce functional systems in appropriate volumes at the right cost to meet society's needs. Bioelectrocatalytic systems will play a key role in this future. In the following section, we will discuss some key publications appearing in the last decade which in the opinion of the authors indicate trends in the development and main achievements in biocatalytic systems for health monitoring.