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The Use of Electrochemical Biosensors in Food Analysis

JOHN BUNNEY, SHAE WILLIAMSON, DIANNE ATKIN, MARYN JEANNERET,
DANIEL COZZOLINO,* JAMES CHAPMAN, AOIFE POWER and SHANEEL CHANDRA

Agri-Chemistry Group, School of Health, Medical and Applied Sciences Central
Queensland University, Rockhampton North, QLD 4702, Australia.

Abstract

Rapid and accurate analysis of food produce is essential to screen for species that may cause significant health risks like bacteria, pesticides and other toxins. Considerable developments in analytical techniques and instrumentation, for example chromatography, have enabled the analyses and quantitation of these contaminants. However, these traditional technologies are constrained by high cost, delayed analysis times, expensive and laborious sample preparation stages and the need for highly-trained personnel. Therefore, emerging, alternative technologies, for example biosensors may provide viable alternatives. Rapid advances in electrochemical biosensors have enabled significant gains in quantitative detection and screening and show incredible potential as a means of countering such limitations. Apart from demonstrating high specificity towards the analyte, these biosensors also address the challenge of the multifactorial food industry of providing high analytical accuracy amidst complex food matrices, while also overcoming differing densities, pH and temperatures. This (public and Industry) demand for faster, reliable and cost-efficient analysis of food samples, has driven investment into biosensor design. Here, we discuss some of the recent work in this area and critique the role and contributions biosensors play in the food industry. We also appraise the challenges we believe biosensors need to overcome to become the industry standard.

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Introduction

Food Safety

The issue of food safety has emerged as increasingly significant public concerns worldwide due to sub-quality foods being linked to increased morbidity, mortality, human suffering, and economic burden[1]. Accordingly, in an information-age society where consumer awareness and expectations of safety

CONTACT Daniel Cozzolino d.cozzolino@cqu.edu.au Agri-Chemistry Group, School of Health, Medical and Applied Sciences Central Queensland University, Rockhampton North, QLD 4702, Australia.

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are high, food manufacturers have to meet the need of modern consumers to make informed purchase decisions and their preference for food products with high quality and affordable price, and at the same time, must maintain high-quality standards and assurance of product safety[2].

Matching the end-user compliance with regulatory guidelines on food quality, the instrumentation and scientific industries have responded with continuous improvement and development of analytical methodologies of many analytical methods, liquid chromatography has acquired a role of great importance in a majority of food analysis, as witnessed by the wide range of applications that can be found throughout the whole literature[3-5]. However, choromatographic analysis is constrained by the rigors of often elaborate sample preparation, and homogenization, clean up and then the analytical component of the test to determine a viable concentration[4]. Consequently, the process often must be repeated multiple times, as many samples are needed to give an accurate result due to the number of interferences in the matrix extracts, which can result in inaccurate identification and false positives[6]. Additionally, the extensive set-up and extraction / clean-up processes required for HPLC analysis can cause prolonged delays in contaminant identification[7]. This hefty time requirement makes HPLC methods unsuitable for "fresh foods" which are typically consumed in a short period, given short shelf lives. It is possible that by the time a contaminant is detected, multiple individuals may have been exposed to it, increasing likelihood of contamination[8,9].

The need for selective measurement of analytes in food is paramount[10]. Here, "younger" technologies like those on an electrochemical platform may present viable alternatives. Biosensors are an examples of new, innovative methods to tacking old but important problems in a quality-conscious society and have become powerful instruments in clinical, environmental and especially, food analyses[11].

Therefore, in this review, we appraise biosensors applied to food analysis. We will examine the attributes of biosensors that present attractive alternatives to traditional technologies and instrumentation, briefly explore recent advances in biosensor technologies and also critique their limitations. We conclude the review by proposing future directions and challenges that the biosensor research arena has to overcome to establish as the new order in food analysis and safety.

Biosensor Attributes

A biosensor can be defined as an analytical device that combines a biologically sensitive recognition element (such as antibodies, nucleic acids, enzymes, organelles, whole cells and aptamers) immobilized on a physicochemical transducer, and connected to

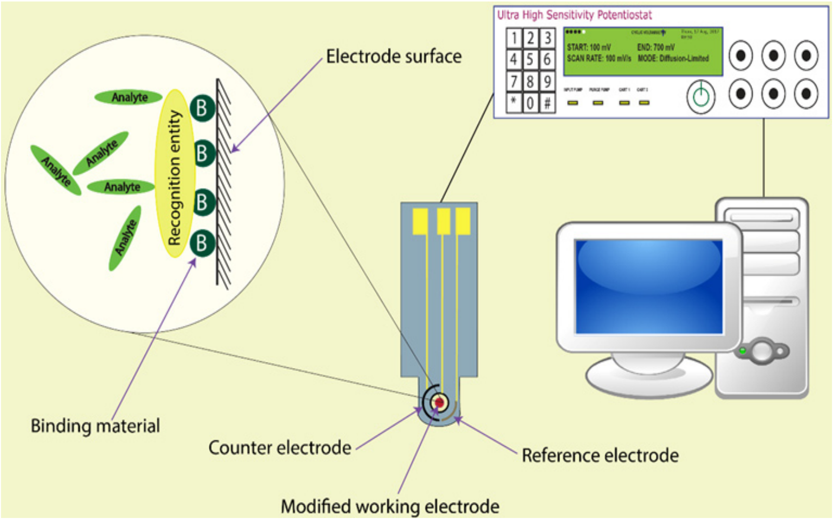

Fig. 1: A simplified, general scheme of a biosensor depicating the three electrode system, direction of electron transfer on the working electrode and a close-up of the working electrode interface with the recognition entity. Reproduced with permission from Ref.[14]

a detector to identify the presence of one or more specific analytes, their concentrations, and kinetics in a sample[12]. Electrochemical biosensors use an electrode transducer to detect electrons released by the reaction of the bioreceptor and analyte to obtain a measurable analysis of the contaminant[13]. Figure 1 shows the general scheme of a biosensor.

Key to the operative success of biosensors is their biological recognition elements which imparts a superior level of specificity and binding affinity with the target molecule. Such binding is termed specific binding or coupling and determines if an interaction occurs, which creates the electrical signal that is recorded and amplified[14]. Because of the particularity of the recognition entity toward the analyte, a high level of selectivity is achieved which results in signals generated solely from such precise interactions, irrespective of the matrix complexity[15]. This is terrifically illustrated by, commercially available, glucose meters that exploit a working electrode modified with glucose oxidase ensuring that a response is solely derived by glucose[16].

The demand for high-speed, accurate and selective identification of analytes present within food produce, such as pathogenic bacteria[17], pesticides[18] and toxins[19], has facilitated rapid advances in biosensor development and enabled quantitative detection and screening. Apart from their inherent specificity, these biosensors help address the multifactorial food industry challenge of high analytical accuracy in the midst of the complex food matrices, overcoming differing densities, pH and temperature[20]. It has been argued that for biosensor use to become widespread, they need to offer further substantial benefits over existing methods[21]. One such advance is the potential for sensor miniaturization, which results in the sensor requiring greatly reduced sample sizes or volumes. However, sensor miniaturization has only partially been achieved to date[22] due to limitations in the structural integrity of very fine electrode tips associated with microelectrodes[23,24].

The recent development of novel bio-recognition molecules, such as synthetic aptamers, DNA, proteins and viruses has enabled considerable selectivity in analysis[25,26]. Furthermore, parallel improvements in the immobilization of bio-recognition molecules[27] through robust attachment methods like electrodeposition[28,29] and nanoparticle-bound entities at the working electrode interface is a significant step in the increased application of biosensors in food analysis. This is due in no small part to their greater specificity, selectivity and affinity for their target analytes[25,26].

New Leaps in Biosensing

The field of biosensors has certainly witnessed astonishing growth in recent times. Over the last three decades, the number of papers published on the subject each year has increased/risen approximately 4000%[30]. Biosensor development and construction has focused predominantly on clinical research, continuing on the pioneering efforts of Clarke in 1950's and 60's[31,32]. Yet, a shift in biosensor focus towards food analysis has grown in the last decade due to the improved accuracy in target pursuit, intensifying demands about quality from stakeholders, such as safety regulators, traders and consumers as well as significant reduction in analysis times associated with electrochemical detection[33].

In the agriculture and food industries, early detection and sensitive analysis of potential contaminants and toxins is crucial[34] and driven by a multiplicity of factors, such as the short shelf life of many fresh food products[35], increasing consumer preferences for chemical free and unprocessed foods[36], minimization of waste/reduction of costs in processing operations[37], and the need for detection in very low quantities, and removal of pathogens from the supply chain that may cause serious illness to the consumer[38].

These pressures are exacerbated by the inherent limitations of traditional food analysis methods that involve expensive, cumbersome instrumentation[39] and as a result, have helped shape biosensor development relating to food analysis[40]. Naturally, researchers have recognized the need for inexpensive, portable sensors that can perform rapidly and accurately with great sensitivity[41].

Food Analysis Challenges

Biosensors address three broad categories of food analysis expectations: safety, quality and authenticity[42]. Food safety screening focuses on the detection of undesirable contaminants in food, such as pesticide and antibiotic residues[43,44], allergens[45], biological toxins[46] and pathogenic microbes[47]. Similar analysis is also used to establish or confirm the nutritional value of a food product[48]. Authenticity analysis seeks to confirm the origin and/or production process of a food stuff, while also providing information about the adulteration or counterfeiting of food[48,49]. The literature indicates that presently, electrochemical biosensors are primarily being utilized in food safety rather than quality and authenticity analysis[50,51].

Traditional analysis methods for detecting harmful microorganisms, such as pathogenic *Escherichia* and *Salmonella*[52], aflatoxins[53] and pesticides such as organophosphates and carbamates[54] could only be conducted post-production. This limitation is easily overcome by the use of biosensors which allows food items to be tested at all phases of production[52] from raw materials screening to the product on shelf, resulting in more efficient means of ensuring of food safety and outbreak prevention[55].

Timeliness and Costs

Improved analysis times is another benefit to biosensor application in food analysis. Using an array of biosensors on a microfluidic or lab-on-a-chip platform, low volume samples can be analyzed directly, thus eliminating the need for laborious and costly sample preparation stages[56]. This is a particularly attractive feature of biosensors, where toxin accumulation often correlates with time[57], for example, mycotoxins are harmful carcinogenic metabolites produced by mold which affects many food products, including but not limited to; bread, cereals, dried fruit, wine and meat products[7].

Biosensors present an attractive alternative as their capability of being used *in situ* allows reduced detection times, from several days to hours, or

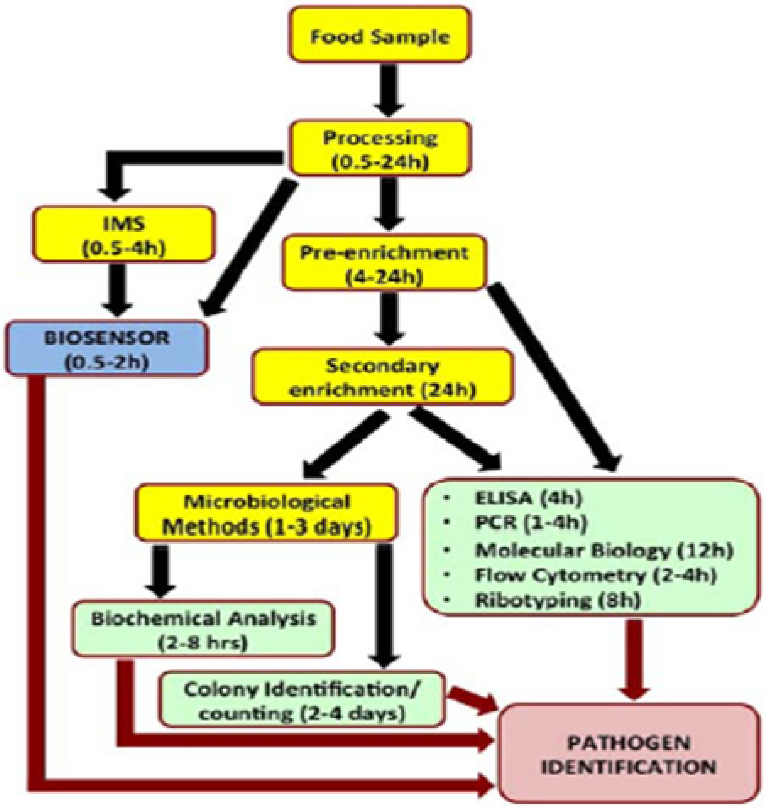

Fig. 2: A flowchart elucidating the processing steps involved and relative time taken in detecting a pathogen in a food sample. reproduced under license from Ref. [67]

even minutes[58-60] as illustrated in Figure 2. Other advantages stemming from in-situ determination capabilities include minimized sampling protocols, reduced storage requirements and the removal of often elaborate sample preparation procedures[61]. Furthermore, in-situ detection capabilities allow for the improved portability of analysis tools such as handheld detection devices which generally require minimal training to operate[62] and can facilitate the integration of real time analysis in food processing work centers/systems[63]. Improved timeliness within food processing systems can also reduce spoilage, particularly in fresh produce, such as seafood, this was illustrated by the development of for the rapid detection of Vibrio parahaemolyticus[64] - a leading global cause of bacterial gastroenteritis. Whilst bacteriophages have been successfully used to remove antibiotic strains of V. parahaemolyticus from seafood[65], the method lengthens the time between catch and plate, thus reducing the seafood's freshness and ultimately its value[66].

The cost effectiveness of biosensors cannot be overstated. The rapid analysis rendered from biosensing allows significant gains through cost mitigation normally reserved for sample preparation methods and the need for expensive laboratories with highly trained staff[68], and the additional possibility of automated on-line analysis in food processing plants69 which will further reduce cost. Moreover, the ability of biosensors to detect contaminants in raw foods in real-time with high specificity and very low concentrations reduces waste[55] and the economic costs associated with health issues and product recalls[67].

Losses Due to Sample Preparation

A fundamental prerequisite to using traditional methodologies in food analysis is the sample homogenization process, which can be problematic because of the organic acids and antimicrobial compounds present in many fruits and vegetables[70]. The release of these compounds during sample preparation can inhibit the detection of certain contaminants, potentially having detrimental impacts on product consumers, a problem not encountered by biosensors as they require little or no sample preparation[8]. Methods commonly used for detecting pathogenic bacteria detection in foods, such as enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) or cell culture[71] are incredibly time consuming. The identification of certain pathogens may take days as they have lengthy sample preparation times coupled with low sensitivity, which can often result in false positives: ELISA requires a 24-48 hr period to successfully detect harmful pathogens such as *Escherichia coli*, a leading cause of death in children under five[72]. Target-induced aptamer displacement strategies can overcome the time and sensitivity barriers by completing the test within 3.5 hours at a sensitivity of 112 CFUmL-1 in a phosphate buffer saline and 305 CFUmL-1 in a milk solution[73]. This far exceeds the sensitivity of ELISA for *E. coli* detection.

Biosensor Detection Process

Despite the ubiquity of microbes, their detection in food is difficult[74] and further complicated by the fact that only some strains are pathogenic[75]. Therefore, screening for the presence of bacteria alone is insufficient for food safety analysis and ideally, only the pathogenic strains, such as *E. coli* is one of two pathogenic strains responsible for 5 food poisoning deaths in Japan in 2011, should be identified[76]. Here, biosensors present notable advances compared to traditional analysis methods in targeting only the analyte, such as the enterohaemorrhagic *Escherichia coli* strain O111[73].

It should be noted that the specificity of biosensors is not limited to the detection of a singular analyte. Several biosensors have been developed to detect minute levels of multiple pesticide residues in foods based on the biochemical pathways the pesticides act upon, such as acetylcholinesterase (AChE) inhibitors. This means biosensor usefulness can extend to an entire class of pesticides[77]. Similarly biosensors have been designed to detect certain compounds or toxin vectors, because of their inherent potential for inducing acute toxicity. Screening for these is critically important to food safety as such contaminants may have devastating effects even in very low concentrations. For example as few as ~10 bacteria can cause infection[67]; carbamate pesticides which, despite having a low bioaccumulation potential are considered carcinogenic[78], and antibiotic residues in animal-derived foods can cause allergic reactions and even secondary infections[79]. Biosensors can also detect traditionally challenging 'viable but not culturable' (VBNC) bacteria, differentiating dangerous pathogens that are in a state of dormancy from non-living, non-threatening bacteria[80].

Current Innovations in Biosensor Design

While enzymatic biosensors were recognized as a leap into elevated or ultimate selectivity, the next stage in biosensor design includes gene based sensors involving DNA; as the recognition or coupling entity (via hybridization), antibody or antigen based biosensors; and whole cell sensors[81]. Within the agri-food industry, pathogen detection trends have focused on the utilization of single sensor platform for detection of multiple pathogens/toxins[82]. More recently, biotechnology has shifted into ever smaller systems to allow for portability, cost reduction, analysis time reduction and commercial viability[83]. Improvements in microfabrication systems have similarly aided in advancing biosensor technology and utility[84]. Emerging nanomaterials, such as nanoparticles and nanofibers have featured in these, paving the way for this miniaturization trend[85].

Such functional nanomaterials enhance electrochemical biosensors in two ways: refining the response features of the electrode by increasing its surface area for instance and assisting in robust attachment of the bioreceptor/recognition entity. With greater surface to area volume ratios, nanomaterials lend greater catalytic prowess, ensure biocompatibility and achieve lower mass transfer resistance. This translates to improved selectivity, sensitivity, time efficiency and cost effectiveness for the biosensor[86-88]. Similarly, the increase in transducer surface area delivers greater conductivity and sensitivity, promotes greater interaction capacity[89] and lowers detection limits[90]. These are all ideal features of a biosensing interface. An excellent example of a nano-biosensor, capable of pesticide residue detection in concentrations as low as 0.4 pM, has been reported in by Verma *et al.,*86. Furthermore, the inclusion of other nanomaterials at the transducer level, for example carbon nanotubes[91], can increase electron transfer and increase the transducer activity[92]. Evidence of these improvements is in the slow but gradual replacement of traditional enzyme-substrate biosensors by nano-biosensor technology[93]. Nano-biosensors have been developed for the agriculture and food processing industries to identify and quantify pesticides, herbicides, pathogenic microorganisms and other microbial contamination such as viruses and bacteria, hormones, glucose, as well as the presence of insects or fungus[94-96].

Another medium of interest is microfluidics which provides throughput processing, reduces sample and reagents volume (down to the nanolitre)[56], increases sensitivity, and employs a single platform for both sample preparation and detection[97]. Microfluidics are portable, disposable, offer real-time detection, and simultaneous analysis of different analytes in a single device with exceptional accuracy[98,99]. For example, microfluidic nano-biosensor for the detection of pathogenic species like *Salmonella* have already been proposed recently[100].

It is envisaged that the ever improving analytical properties of electrochemical transducers will even allow for the detection of multiple analytes simultaneously[101]. However, despite these promising advances and the potential of nanomaterial-based biosensors, realistically their application within food matrices is still in the very early stages of development[102]. Compared with other biosensing forays, for example in medicinal biosensor technology through favored point of care and home diagnostics for pregnancy, glucose content, biosensing in food production and processing or screening has not been embraced as readily[103-105.]

Concluding Remarks and Future Directions

Although biosensors display clear advantages over traditional methods, the perfect biosensor does not as yet exist[106] and there are many obstacles in its development to be overcome[107]. Presently, many biosensors are not easily implementable, if only because so few are currently available commercially[107].

Nonetheless, it is almost inevitable that the future of biosensors will involve partnership with information communications technology to assist food producers, retailers, authorities and even consumers, in their decision making108 by equipping them with the necessary tools and data to improve their decision-making process. This will ultimately, enable greater management of the natural resources[109-112]. Moreover, inspired by mammalian sensory networks, new sensor systems being developed have the potential to revolutionize food analysis[113,114]. Biomimetic sensors, such as electronic tongues and electronic noses are based on biosensor technologies[115] and we expect that their exploitation of arrays of low specificity sensors capable of detecting multiple signals will allows a more complete analysis of food quality. Inspiration for these developments and applications comes from the electronic tongues that form the basis for food authenticity and safety sensor systems[116,117], or similarly, electronic noses that can detect unique volatile compounds within the tea, wine, coffee, and spice industries[118-120].

The combination of different types of biosensors has great promise: the fusion of electronic tongues with electronic noses and may further increase the identification capabilities of such a biomimetic system, as precisely as it does within the biological system[121]. The advantage of real time monitoring in food manufacture, especially of dairy products[122] and brewed products[123], further enhances the usefulness of biosensors and drives the push for their commercially availability to general public[124]. The inherent specificity, sensitivity, and adaptability of biosensors make them the ideal candidate for use as a safety net throughout the food industry improving product quality with minimal investment[124], both now and for the foreseeable future. The opportunity afforded through biosensing, particularly in situ and safety analysis at all levels of the supply chain, as well as authenticity and quality analysis by the consumers themselves, make biosensors food productions tool of the future.

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