Journal of Microbiological Methods 95 (2013) 48–56

Contents lists available at ScienceDirect

Journal of Microbiological Methods

journal homepage: www.elsevier.com/locate/jmicmeth

Campylobacter spp. detection in the 21st century: A review of the recent achievements in biosensor development

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ARTICLE INFO

Article history:
Received 6 December 2012
Received in revised form 18 April 2013
Accepted 10 June 2013
Available online 2 July 2013

Keywords:
Biosensors
Optical
Electrochemical
Mass sensitive
Campylobacter spp.
Review

ABSTRACT

Campylobacter spp. are an important cause of acute bacterial diseases in humans worldwide. Many bacterial species in the *Campylobacter* genus are considered harmful and may cause several infectious diseases. Currently, there are no commercial biosensors available to detect *Campylobacter* spp. in food matrices, and little to no testing has been done in research laboratories with actual food matrices. Biosensors potentially provide a powerful means to detect *Campylobacter* spp. with the advantages of high sensitivity (low limits of detection with a high signal to noise ratio), high specificity (able to selectively detect the target among several similar targets), real time sensing, and in-site monitoring. This review summarizes the latest research in biosensing technologies for detection of *Campylobacter* spp. based on a variety of transducers and recognition elements. Finally, a comparison is made among all recently reported biosensors for the detection of *Campylobacter* spp.

1. Introduction

Campylobacteriosis is an infectious disease typically affecting the digestive system caused by bacteria of the genus *Campylobacter*, and is symptomatically characterized by diarrhea, cramping, abdominal pain, and fever. The *Campylobacter* cell is characterized by a large spiral structure and the minimum infectious dose is around 500 cells, with a typical incubation period of two to five days, however, it can manifest within 10 days of exposure (Che et al., 2001; Sapsford et al., 2003). Campylobacteriosis is considered one of the most common causes of diarrheal illness in the United States and affects an estimated 2.4 million people each year, representing about 0.8% of the population. While typically non-lethal, approximately 124 people die each year from *Campylobacter* infections. There is also evidence that campylobacteriosis can lead to Guillain–Barré syndrome, in which as many as 40% of those cases may have been triggered by Campylobacteriosis (Houliston et al., 2007). The worst recorded outbreak in the United States occurred in 1978 in Vermont, where over 2000 people were infected (Walker et al., 1986). Not only do these bacteria cause very inconvenient symptoms for the victim, but it also costs the economy in productivity due to missed work, and also in medications and treatment (Palchetti and Mascini, 2008; Skirrow and Blaser, 2000).

Campylobacter jejuni is the most common cause of human illness; however other species can be just as dangerous, such as *Campylobacter coli*. Both of these species have adapted to thrive in poultry. Typically transmission of the infectious disease occurs through eating contaminated food, especially poultry, drinking contaminated water, or having contact with an infected animal, including domestic animals and pets. The challenges associated with these bacteria include decreasing the amount of contamination, prevention and reduction of the development of resistant strains, and detection of cases and outbreaks (CDC, 2010).

There are many conventional detection methods available including plating/culturing, enumeration methods, biochemical testing, microscopy, as well as newer methods such as immunoassays, PCR/hybridization, mass spectrometry and DNA probes. There are even a few widely available identification kits. These methods can, however, be time-consuming, require exhaustive sample preparation, expensive, or have poor selectivity (Deisingh and Thompson, 2004; Ivnitski et al., 1999; Van Dorst et al., 2010a, 2010b). Biosensors offer some marked advantages over traditional methods, including, but not limited to, time-efficiency, cost-effectiveness, real-time sensing, in-situ monitoring, and specificity, while maintaining reasonable sensitivity (Ivnitski et al., 1999; Van Dorst et al., 2010a, 2010b). While biosensors have provided a means of circumventing many of these disadvantages, there are still improvements that must be made before their implementation can be fully realized (Ivnitski et al., 1999). The incorporation of nano-materials into design, fabrication, and implementation of biosensors has some promising results, and these effects will be addressed later (Gallardo and Amanda, 2009; Pérez-López and Merkoçi, 2011).

The biosensor research and development community are devoting their efforts to provide the means to accurately and rapidly detect the

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http://dx.doi.org/10.1016/j.mimet.2013.06.023

presence and quantity of *Campylobacter* bacteria (Alocilja and Radke, 2003; Arora et al., 2011a,b; Bhunia, 2008; Che et al., 2001; Deisingh and Thompson, 2004; Hall, 2002; Lazcka et al., 2007; Leonard et al., 2003; Sista et al., 2006; Wei et al., 2007). Biosensors based on recognition elements, such as DNA, aptamers, antibodies and bacteriophages, and transducers of optical, electrochemical, and mass sensitive types have shown some promise in detecting food-borne pathogens such as *Campylobacter*. This review will discuss the transduction methods and recognition elements of recently developed sensors for the detection of the different species of the *Campylobacter* genus.

2. Biosensors for analysis of *Campylobacter* spp.

A sensor is *a device capable of generating a signal for the detection or measurement of a physical property to which it responds*, as defined in the Oxford English Dictionary (OED, 2012). In general, a sensor consists of the recognition element, the transducer, and the signal processor (Eggins, 2002a,b). The recognition element responds to the specific analyte, and the response is converted by the transducer into a signal decoded by the signal processor. Sensors can be divided into three groups, namely, physical sensors, chemical sensors, and biosensors (Eggins, 2002a,b). Biosensors have diverse classifications, but all of them incorporate biorecognition elements such as nucleic acids, enzymes, antibodies, bacteriophages, or even whole cells (Borisov and Wolfbeis, 2008). Many good books and reviews cover the research of biosensors (Borisov and Wolfbeis, 2008; Griffin and Stratis-Cullum, 2009; Ligler et al., 2007; Rasooly and Herold, 2011; Taitt et al., 2005), and their applications in the detection of pathogenic bacteria (Deisingh and Thompson, 2004; Lazcka et al., 2007; Nayak et al., 2009), early warning against bio-warfare agents (Shah and Wilkins, 2003), and in food safety (Alocilja and Radke, 2003; Arora et al., 2011a,b; Bhunia, 2008; Hall, 2002; Luong et al., 1997; Palchetti and Mascini, 2008; Patel, 2006; Pérez-López and Merkoçi, 2011; Velusamy et al., 2010a, 2010b; Warriner and Namvar, 2011). Many different biosensors have been developed for the analysis of *Campylobacter* spp. Some have even been tested with different food matrices.

2.1. Optical biosensors to detect Campylobacter spp.

Optical transducers have played an important role in biosensors over the last three decades (Balasubramanian, 2008; Ligler and Rowe-Taitt, 2002). They are advantageous due to their high sensitivity (Brecht and Gauglitz, 1997), real-time and non-destructive detection, and the utilization of an evanescent wave that is sensitive to sensor-analyte interfaces. Optical biosensors can be subdivided into Absorbance, Fluorescence, Reflectance, and Light scattering types. In the Reflectance, three widely used methods are surface plasmon resonance (SPR), total internal reflection fluorescence (TIRF, e.g., array biosensor), and attenuated total reflectance (Eggins, 2002a,b; Ramanathan, 2010). SPR and TIRF will be discussed in detail below, as well as the light diffraction system, which is similar to the reflectance system and is not commercially available, but has been utilized in many research laboratories.

2.1.1. Structure of SPR biosensors

The phenomenon of SPR was explained by Fano in 1941. The excitation of surface plasmons was observed by Powell and Swan in 1960, the famous configuration to realize that excitation was stated by Kretschmann in 1971, and in 1990 Biacore AB fabricated the first commercial SPR instruments (Homola et al., 1999; Sharma et al., 2007). A commercial integrate SPR chip from SensiQ (SensiQ Technologies, Inc., Oklahoma City, OK) is presented schematically in Fig. 1a.

In the SPR method, a thin metal film, such as 50 nm Au, is deposited onto the prism surface. An incident light beam travels inside prism and is totally reflected on the metal-prism interface, which yields an evanescent wave that travels through the Au film. At the boundary of the metal film, electrons behave in a quasi-free manner (Eggins, 2002a,b). They could be excited by evanescent wave and experience charge oscillation, i.e., the surface plasmon (SP). The surface plasmon extends into space along with evanescent wave. The excitation of SPs occurs when the charge oscillation couples to the component of the wave vector of plane polarized incident light, which is called surface plasmon resonance (SPR) (Fig. 1b). When surface plasmon resonance occurs, part of the incident light energy is converted into an evanescent wave and thus decreases the intensity of reflected light. This decrease varies with different incident angles. In most commercial devices, a range of incidence angles are used and a curve of reflectivity vs. angle of incidence θ is obtained (Fig. 1c, d). A resonance dip, where the reflectivity is minimum, occurs at the pseudo-Brewster angle (Eggins, 2002a,b), also called "SPR angle."

This resonance dip angle is sensitive to minimal changes of the metal-analyte interface, which is determined by the change in refractive index (RI) of the bulk analyte solution, the surface adsorbed bio-materials and their coverage density and thickness. Normally, 1 $\Delta\theta$ (the SPR angle change) $\approx$ 0.01 RIU (refractive index units) is applied in commercial devices, and 1 RIU $\approx$ 1 μg/mm^2 attachment of protein (Stenberg et al., 1991). RU (resonance unit) is most commonly used and equals 10^{-6} RIU, and thus 1 RU $\approx$ 1 pg/mm^2 attachment of protein. The curve of RU vs. time is usually obtained in a SPR device (Fig. 1e, f), which can be used to qualitatively and quantitatively analyze the binding of bio-materials in a real-time and label-free manner of detection.

2.1.2. SPR biosensors for Campylobacter detection

SPR biosensors have the advantages of high sensitivity, real-time, label free, and need of minimal amounts of reagents (Dudak and Boyacı, 2009; Homola et al., 2008; Lane et al., 2011). These sensors have been widely used for the detection of *Campylobacter* spp. in research studies (Houliston et al., 2007; Lane et al., 2011; Sista et al., 2006; Taylor, 2008; Taylor et al., 2006; Wei et al., 2007). The first SPR biosensor for real-time detection was described by Sista et al. (2006) using the commercial product Spreeta™ dual-channel SPR sensor. Using the avidin–biotin chemistry, a polyclonal rabbit IgG antibody for *C. jejuni* was immobilized on sensor surface. Bovine serum albumin (BSA) was used to block any non-specific bindings. The authors stated a detection range from 10^2 to 10^9 cfu/ml, and similar response to *C. jejuni* in PBS buffer and milk. Using the same device setup Wei et al. (2007) detected *C. jejuni* in pure culture and inoculated broiler rinse samples. The authors stated a detection limit of 10^3 cfu/ml. While the response was similar for *C. jejuni* in pure culture and rinse samples, the high background from the latter reduced the overall sensitivity of the assay.

By utilizing the antibody-antigen binding, Taylor et al. (2006) applied an eight-channel SPR sensor to detect *C. jejuni* in buffer at pH 7.4, apple juice at native pH 3.7, and apple juice at an adjusted pH of 7.4. Glass chips were used as substrates and were deposited by vacuum evaporation with 2 nm Cr and 55 nm Au, and then functionalized with a self-assembled monolayer (SAM) of biotinylated alkanethiol:oligo(ethylene glycol) (BAT:OEG), followed by the addition of streptavidin and then biotinylated polyclonal rabbit antibody (PAb) for *C. jejuni*. Potentially, all of eight channels were able to be functionalized with different antibodies and enable simultaneous detection of multi-analytes. The limit of detection (LOD) was 1.1×10^5 cfu/ml in PBS, and was similar in apple juice. Increasing the pH of apple juice enhanced the sensor response, which might be explained by the pH dependence of antibody–antigen binding (Gibas et al., 2000; Taylor et al., 2006).

C. jejuni has also been detected with the use of the receptor binding protein (RBP) of *Campylobacter* bacteriophage NCTC 12673 (Singh et al., 2011). Gold coated glass chips (5 nm Cr, 25 nm Au) were functionalized with glutathione SAM for the immobilization of the RBP.

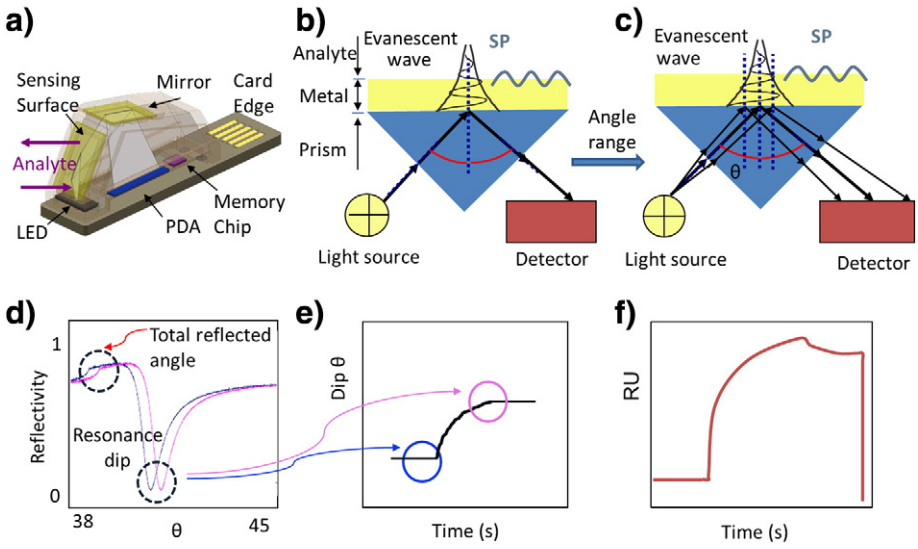

Fig. 1. The mechanism of SPR sensing technique. (a) Schematic representative of the commercial SensiQ SPR chip (from the company demonstration). (b, c) Schematic representative of the working mechanism of SPR. (d, e, f) Curve of RU vs. time is usually obtained instead of reflectivity vs. θ.

BSA was used as the blocker. The authors found that the oriented attachment of RBP due to the glutathione SAM resulted in twice or more bacterial capture ability comparing with dithiobis (succinimidyl propionate) SAM. *Salmonella* was used to confirm the specificity, which yielded an insignificant response. The authors stated that, as the logarithm of concentration was used, the linear range of detection was 10^2–10^8 cfu/ml with the fitting variation $R^2 = 0.99$, and the LOD = 10^2 cfu/ml.

Besides direct detection of *Campylobacter*, SPR could be used to study the binding interactions of bacteria and their respective antibodies, through sugar analogs. Houliston et al. (2007) studied the interactions of four monoclonal antibodies from sensitized mice with oligosaccharides, which are similar as that synthesized inside the cell of *C. jejuni*. Lane et al. (2011) studied the interaction between oligosaccharides and *C. jejuni* with the aid of biotin capture reagent. All of these studies are helpful to optimize the SPR biosensors and create anti-infective medicines for pathogenic bacteria.

2.1.3. Total internal reflection fluorescence (array biosensor)

In addition to SPR, the evanescent wave created by light total reflectance can be used to excite the fluorophores. The evanescent wave-excited fluorescence was first described by Hirschfeld (1965), and in 1975, Kronick and Little (1975) used for the first time the fluorescence immunoassay for biosensing. A main application of the excited fluorescence is the Array Biosensor, which was developed by Feldstein et al. (1999) at the Naval Research Laboratory (NRL) to address the need of rapid detection of multiple bio-threat agents. Basically, an Array Biosensor can be divided into the fluidics, optics, waveguide cladding, and data processing units (Feldstein et al., 1999; Golden et al., 2004). The optics unit consists of a laser source and a set of mirrors that lead the light to the waveguide cladding at a specific incident angle for total reflectance, which results in the creation of evanescent wave. The waveguide cladding is a microscope slide modified with the array of fluorophores conjugated bio-probes, such as antibodies, for the analyte, which flows in the fluidics unit. Fluorescence is excited from the fluorophores by the evanescent wave, and is influenced by the interaction between the bio-probes and the analyte. A charge coupled device camera, included in the data processing units, records the filtered fluorescence. By this setting, the Array Biosensor is capable of real-time monitoring the flow of analytes. The setup of an Array biosensor is shown schematically in Fig. 2.

Since its development, significant progress has been made by using the Array Biosensor for detecting multiple agents such as organophosphates, the naturally occurring protein ricin, the oligomeric protein complex cholera toxin, ochratoxins, staphylococcal enterotoxin B, bacteria, such as *Bacillus anthracis*, *C. jejuni*, *Shigella flexneri*, etc. (Bakaltcheva et al., 1999; Benecky et al., 1998; Edelstein et al., 2000; Ngundi et al., 2005; Ramanathan, 2006; Ramanathan and Simonian, 2007; Rowe-Taitt et al., 2000a,b; Sapsford et al., 2004; Shriver-Lake and Ligler, 2005; Shriver-Lake et al., 2003; Wadkins et al., 1998). For a recent review of Array Biosensors, readers are encouraged to read Ligler et al. (2007).

Sapsford et al. (2004) demonstrated the ability of the sensor with a sandwich immunoassay to detect multi-biohazards including *C. jejuni* and *C. coli* in buffer as well as complex food matrices. In this sensor, the monoclonal rabbit antibodies for *C. jejuni* were biotinylated by using the EZ-link biotin-LC-HNS and labeled by Cy5 bisfunctional dye, and then patterned onto the glass waveguide using poly(dimethyl)siloxane flow cells. The *Campylobacter* sandwich immunoassay format responded to both of *C. jejuni* and *C. coli* in PBS buffer, turkey, carcass wash, milk, and lettuce leaves. As shown in Table 1, for *C. jejuni* in PBS plus Tween and BSA (PBSTB), river water, ground turkey, and carcass wash, the linear range was R^2 = 0.97, 0.99, 0.998 and 0.97, respectively. For *C. coli* in the same four substrates, the linear range was R^2 = 0.98, 0.98, 0.94 and 0.94, respectively. The LOD in all cases was the lower limit of the linear range. Using the same experimental setup, the ability of detecting *C. jejuni* in buffer and complex food matrices has been demonstrated (Sapsford et al., 2006a,b). The LOD was 10^2 to 10^3 cfu/ml for the

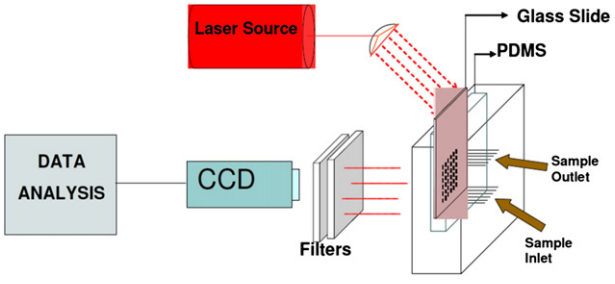

Fig. 2. Schematic representative of Array biosensor (Ramanathan and Simonian, 2007).

Table 1
Overview of biosensors to *Campylobacter* spp. divided by the type of transducer.

Transducers		Detector components	Recognition element	Analyte	Matrix	Analytical range (cfu/ml)	LOD (cfu/ml)	References
Optical	SPR	Spreeta™, Avidin, biotinylated polyclonal rabbit IgG antibody.	Antibody	*C. jejuni*	PBS and milk	10^2–10^9	?	Sista et al. (2006)
				C. jejuni	PBS and meat	10^3–?	?	Wei et al. (2007)
		Glass chip with 2 nm Cr + 55 nm Au, SAM of BAT:OEG, streptavidin, and biotinylated PAb.	Antibody	*C. jejuni*	PBS and apple juice	10^5–10^7	1.1×10^5	Taylor et al. (2006)
		Glass chip with 5 nm Cr + 25 nm gold, glutathione SAM, RBP. BSA as blocking agent	RBP	*C. jejuni*	PBS	10^2–10^8	10^2	Singh et al. (2011)
		Spreeta™, thiolated DNA probe	DNA	*hipO*	PBST	?	2.5 nM	Gnanaprakasa et al. (2011)
	TIRF	Array biosensor, glass slide, biotinylated monoclonal rabbit antibody, Cy 5 dye.	Antibody	*C. jejuni*	PBSTB	10^3–8×10^3	10^3	Sapsford et al. (2004)
					River water	3×10^3–10^4	3×10^3	
					Turkey	1.6×10^3–10^4	1.6×10^3	
					Carcass wash	3×10^3–10^4	3×10^3	
				C. coli	PBSTB	8×10^5–3×10^6	8×10^5	
					River water	1.6×10^6–3×10^6	1.6×10^5	
					Turkey	8×10^5–3×10^6	8×10^5	
					Carcass wash	8×10^5–3×10^6	8×10^5	
				C. jejuni	PBSTB	?	10^3	Sapsford et al. (2006a,b)
					Yogurt		2×10^3	
					Milk		5×10^2	
					Turkey sausage		5×10^2	
					Turkey ham		4×10^3	
	Diffractive	DotLab®, biotinylated DNA probe	DNA	*hipO*	PBST	?	5 nM	Gnanaprakasa et al. (2011)
	Fluorescence	Au NP, MPA and Hcys, dye Rhodamine B, ss-DNA.	DNA	DNA	PBS	7×10^4–0.8 nM	?	Darbha et al. (2008)
Electrochemical	Amperometric	Magnetic beads, streptavidin, biotinylated rabbit antibody, phosphatase labeled, phenyl phosphate, tyrosinase modified CPE (indirect detection)	Antibody, phosphatase	*C. jejuni*	PBS, turkey carcass wash	10^2–10^7	2×10^4	Che et al. (2001)
		SS electrode, BLM, antibodies, (ion channel)	Antibody	*Campylobacter* spp.	Acetate buffer	?	1 cell (expected)	Ivnitski et al. (2000)
		(SWASV) SPE, CA-MWCNT, antibodies for C. spp., NC (indirect detection)	Antibody	*Campylobacter* spp.	Milk	1×10^3–5×10^5	4×10^2	Viswanathan et al. (2012)
	Impedimetric	GCE, OCMCS-Fe_3O_4, antibodies 2D12 for *C. jejuni*, BSA; $Fe(CN)_6^{3-/4-}$	Antibody, $Fe(CN)_6^{3-/4-}$	*C. jejuni*	PBS	10^3–10^7 cfu/ml	10^3 cfu/ml	Huang et al. (2010)
	Conductometric	Electrodes	N/A	*C. jejuni*	Broth medium	1–10^4 cfu/ml	1	Line and Pearson (2003)
Mass sensitive	QCM	Lectins immobilized onto surface, 7 strains of *C. jejuni*	Lectin assay	*C. jejuni*	PBS	?	?	Yakovleva et al. (2011)
		Lectins immobilized onto surface, FIA, several strains of *C. jejuni*	Lectin assay	*C. jejuni*	PBS	10^3–2×10^4 cells	10^3 cells	Safina et al. (2008)

LOD, limit of detection; C. spp., *Campylobacter* species; *C. jejuni*, *Campylobacter jejuni*; *C. coli*, *Campylobacter coli*; *hipO*, *hippuricase* gene uniquely from *C. jejuni*.
Column "Transducers": SPR, surface plasmon resonance; TIRF, total internal reflectance fluorescence; QCM, quartz crystal microbalance.
Column "Detector components": Spreeta™ dual-channel SPR sensor; SAM, self-assembled monolayer; BAT:OEG, biotinylated alkanethiol:oligo(ethylene glycol); Cr, chrome; Au, gold; RBP, receptor binding protein (of *Campylobacter* bacteriophage NCTC 12673 in ref. (Singh et al., 2011)); DotLab® Diffraction Optics Technology system; NP, nanoparticles; CPE, carbon paste electrode; SS electrode, stainless-steel working electrode; BLM, bilayer lipid membrane; SPE, screen printed electrode; CA-, carboxylic acid functionalized; MWCNT, multi-walled carbon nanotubes; NC, nanocrystals; SWASV, square wave anodic stripping voltammetry.
Column "Analyte": PBS, phosphate buffer saline; PBST, PBS plus Tween; PBSTB, PBS plus Tween and BSA; BSA, bovine serum albumin.

bacteria in PBSTB, yogurt, milk, ground turkey sausage, and ground turkey ham.

2.1.4. Diffractive optics

Other than total internal reflectance, light diffraction is an alternative method for bio-sensing. The diffractive optics method utilizes the grating-based light diffraction and immobilized capture surfaces. Similar as a SPR device, a prism structure is used, into which a laser travels at a specific angle. The top surface of the prism, which is also the bottom of flow channel, is flat until capture molecules are immobilized on an ordered pattern of lines that form an optimized grating mode. The grating makes the reflected beam a diffraction pattern due to the constructive and destructive interference of light wave. As the analyte flows through the channel, the immobilized molecules, such as antibodies, bind with the analyte, increase the surface pattern height, and cause an increase in the diffraction efficiency as well as the diffraction intensity. Dissociation of the analyte leads to a decrease in corresponding signal. While avoiding non-specific binding in SPR biosensors requires the usage of a blocker like BSA, in diffractive optics method, since non-specific binding does not follow any ordered manner as the initial pattern, it yields insignificant interference to the signal. With the ability of label-free and real-time monitoring, diffraction optics technology has been widely used for detecting live cells (John et al., 1998; Morhard et al., 2000), proteins and small molecules (Mines et al., 2002).

A successful commercial product is the dotLab® system (Axela Inc., Toronto, On, Canada). Gnanaprakasa et al. (2011) used the dotLab system to detect unique DNA segments from *C. jejuni* and obtained comparable results with Spreeta SPR biosensor (Fig. 3). The presence of the *hipO* gene in *C. jejuni* allows for specific detection of this pathogen. Complementary DNA was immobilized onto the dotLab system and SPR biosensor surface and the *HipO* gene was detected from *C. jejuni* cells suspended in PBS plus Tween. The LOD was calculated to be 2.5 nM for SPR and 5 nM for dotLab (Gnanaprakasa et al., 2011).

2.1.5. Fluorescence

Fluorescence resonance energy transfer (FRET), also called Förster resonance energy transfer, resonance energy transfer (RET) or electronic energy transfer (EET), is a widely used method. FRET was first described in 1948 as a non-radiative energy transfer process between two chromophores (Förster, 1948; Valeur, 2001). A photo-excited donor chromophore may transfer energy to an acceptor fluorescent molecule that is within very close proximity (<10 nm). The transfer efficiency is strongly affected by the distance and orientation between the donor and acceptor, which can be determined by a fluorescence emission spectrum (Sapsford et al., 2006a,b). With the aid of fluorescent proteins (FPs) (Shaner et al., 2005), many biological events can be detected in FRET based biosensors. This type of biosensors has been used for the detection of protein binding (Kramer et al., 2006), protein conformational change (Sakai et al., 2001), phosphatase activity (Sato et al., 2002), and metabolic molecules such as glucose (Fehr et al., 2004).

Darbha et al. (2008) developed a miniaturized gold nanoparticle-based FRET probe for screening *Campylobacter* DNA. The authors stated that nanoparticle-based FRET can be used for monitoring the biological events over the distance limit of 10 nm. The gold nanoparticles were prepared from $HAuCl_4$ reduction. After the surface modification with mercaptopropionic acid (MPA) and homocystine (Hcys), the gold nanoparticles were immersed in an aqueous solution of Rhodamine B (a staining fluorescent dye) tagged single-stranded DNA (ss-DNA). The single and double stranded DNAs (ds-DNA) have different electrostatic properties (Ray et al., 2005). The dye, which was tagged on the ss-DNA, was adsorbed onto the gold nanoparticles and the fluorescence was 100% quenched. Once DNA hybridization occurred, the ds-DNA was not as flexible as the ss-DNA, and thus the constrained conformation was changed, which reduced the fluorescence quenching. Monitoring of the fluorescence spectrum was used for detecting the target DNA sequences. The linear range of detection was 8×10^{-1}–7×10^{4} nM of DNA, but no comparison was made to determine the number of *Campylobacter* cells (Darbha et al., 2008).

2.2. Electrochemical biosensors

As a widely used technique (LaGier et al., 2007), electrochemical biosensors have some advantages over other transducing systems. Modern electrochemical techniques have low detection limits (10^{-7}–10^{-9} M, or 30 ppb) for gaseous compounds (Yang et al., 2011, 2012) and require micro-liters of samples. They can be operated in turbid medium, while the turbidity would bring unacceptable background signal for optical sensors and inhibits their

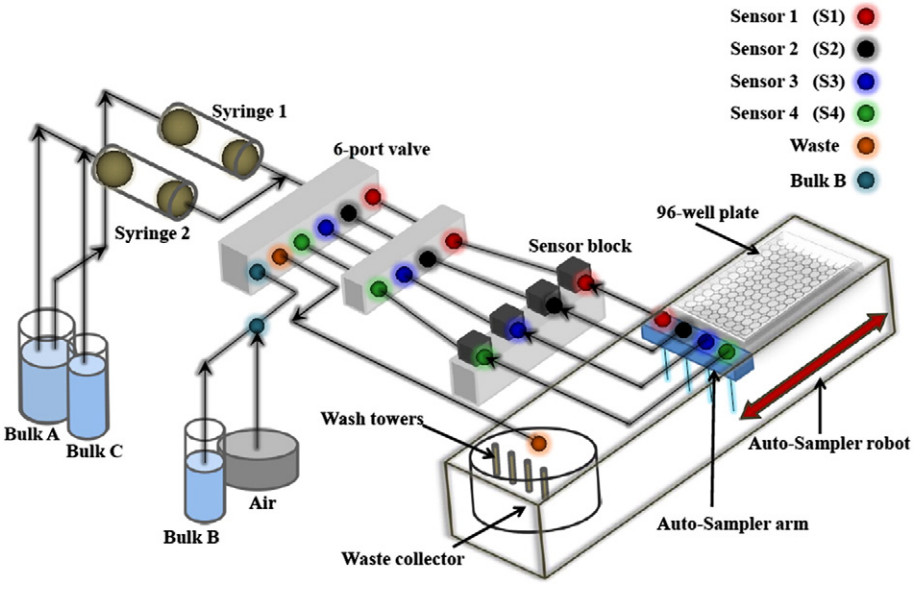

Fig. 3. Schematic representative of the flow path and tubing connections in a dotLab biosensor system (from the ref. (Gnanaprakasa et al., 2011)). 0.032-inch Teflon tubes are used. The flow directions of solution are shown with arrows. The analytes are kept in the respective wells in the order that they have to pass over the sensor surface.

use (Shah and Wilkins, 2003). Other advantages include high sensitivity, rapid analysis, and the possibility of miniaturization. As a result of miniaturization, a small volume of sample can be utilized (Palchetti and Mascini, 2008). Moreover, the continuous response allows in-situ and on-line measurements. The main disadvantage is the low selectivity, which can be overcome by surface modification with specific recognition elements, such as nucleic acids, enzymes, and antibodies.

Electrochemical transducers, which usually consist of three electrodes, convert the interactions of the recognition element with an analyte in solution to an electrical signal that can be processed. The interaction happens at the interface between electrode surface and analyte solution, and produces a change in an electrical phenomenon such as potential, current, impedance, capacitance, etc. Electrochemical biosensors can be classified as amperometric (also voltammetric), impedimetric, potentiometric, and conductimetric (Bard and Faulkner, 1980).

2.2.1. Amperometric biosensors

Amperometric biosensors often utilize three-electrode system; the working electrode, the reference electrode and the counter electrode. The reactions of interest are recorded from the working electrode. Materials to fabricate the working electrode are usually electrochemically inert, such as platinum, gold, glassy carbon and graphite (McCreery, 1991) and boron-doped diamond (Xu et al., 1997). The analyte must be oxidizable/reducible as specific potential is applied to obtain a current vs. potential or current vs. time curve. The most commonly used modes include cyclic voltammetry (CV), linear sweep voltammetry (LSV), and amperometry (Bard and Faulkner, 1980). In CV and LSV, the potential is scanned in a range and the current signal is recorded, while in the amperometry constant potential or potential steps are applied. They work based on the mechanisms of: 1) a chemical substance is reduced/oxidized at a specific potential; and 2) the reduction/oxidation peak current is proportional to the concentration of analyte. Based on the specific interactions of antibody-antigen, enzyme-reagent, or DNA base pairing, modified amperometric biosensors are able to selectively detect most microorganisms (Shah and Wilkins, 2003).

Ivnitski et al. (2000) performed an experiment to detect *Campylobacter* spp. based on the electron transfer through a bilayer lipid membrane (BLM). A stainless-steel (SS) electrode was immersed in the 1:1 squalene–decane solution of egg phosphatidylcholine to form the BLM. The antibody specific to *Campylobacter* was immobilized by soaking the electrode for 5 h. A channel pore remained closed naturally in the antibody but would be interrupted by antibody–antigen binding. The BLM is a dielectric material and impeded the electron transfer to the electrode. The conformation perturbations of the antibody, as the bacteria appeared, "opened a channel" for the ion permeability through the BLM, which yielded a current peak in the amperometric biosensor. The current peaks were always of the same size independent of the cell concentration, which indicated that the channel was either open or closed, while the width of the current peak was determined by the concentration. The current of peaks corresponded to a flow of ~10^{10} ions/s, which suggested that the LOD of this method could be one cell per sample, stated by the author. The selectivity was confirmed by the fact that no response was obtained against the negative control sample with *Escherichia coli* (Ivnitski et al., 2000).

Che et al. (2001) used an indirect amperometric method to measure the *C. jejuni* in PBS, chicken carcass wash water, and ground turkey meat, in which magnetic beads were used to capture the bacteria. Modified magnetic beads were mixed with the bacteria and shaken for 1 h to form bead-bacteria conjugates. Eight types of magnetic beads with different modifications and sizes were compared to achieve the optimal condition for cell capture. After separation from the supernatant, the conjugates were mixed with phenyl phosphate for 1 h to produce phenol. The phenol was detected by a tyrosinase modified carbon paste electrode and the current signal was recorded. The results for the bacteria in PBS and poultry samples were similar. As the logarithm of concentration was used for linear fitting, a linear relationship for the number of *Campylobacter* cells corresponding to signal current can be found in a range of 10^2–10^7 cfu/ml with the fitting variation R^2 of 0.94, and the limit of detection for their system was estimated to be 2×10^4 cfu/ml.

Using the antibody–bacteria–antibody strategy, Viswanathan et al. (2012) detected *Campylobacter* spp. with the aid of nanocrystals. A screen-printed electrode was modified with carboxylic acid functionalized multi-walled carbon nanotubes (MWCNT), followed by the immobilization of antibodies for *Campylobacter* spp. After exposure to fresh bovine milk spiked with *Campylobacter* spp. the electrode was immersed in a solution containing antibody-conjugated PbS nanocrystals to form the antibody–bacteria–antibody sandwich structure. Square wave anodic stripping voltammetry was used to obtain the signal from dissolution of metal ions and a correlation to the number of bacteria. A sigmoidal calibration curve was obtained in the range of 1×10^3 to 5×10^5 cfu/ml, and the LOD was estimated to be 4×10^2 cfu/ml (Viswanathan et al., 2012).

2.2.2. Impedimetric biosensors

The techniques based on impedance are different from amperometrics. In amperometric methods, the system is applied with a large perturbation to make the reactions happen on electrodes. The reactions are driven far from equilibrium conditions by applying potential sweeps or steps, and the transient signals are of interest (Bard and Faulkner, 1980). However, in impedance, the potential applied to the system is often made of a "dc potential," which equals to the equilibrium reaction potential of systems such as a redox pair $Fe(CN)_6^{3-/4-}$ (1:1), plus an "ac potential" which is an alternating potential with a small amplitude, such as 5 mV. Therefore, the system always stays close to the equilibrium state. The advantages included by this mechanism are: 1) the response is stable and can be averaged over a long time range to yield a precise measurement; 2) this technique can utilize the linear I–V relationship around the equilibrium potential indicated by the *current-overpotential equation*; and 3) it can be operated over a wide frequency range such as 10^6–10^{-4} Hz (Bard and Faulkner, 1980). Moreover, impedance-based biosensors have the capability of miniaturization into a chip format (Pedrero et al., 2009).

Recently, many impedance-based biosensors have been used. An impedimetric biosensor has been developed by Louie et al. (1998) for the determination of *E. coli* O157:H7 and *Salmonella* spp. developed. With a platinum thin film involved impedimetric biosensor, De Silva detected *Staphylococcus* enterotoxin B and the corresponding antibody (DeSilva et al., 1995). This type of biosensor has also been used for the determination of DNA hybridization (Bonanni et al., 2008), assessment of cytotoxicity (Ceriotti et al., 2007), and detection of pathogenic bacteria (Yang et al., 2004).

Based on modified Fe_3O_4 nanoparticles, Huang developed an impedimetric biosensor for detecting *C. jejuni* in stool samples (Huang et al., 2010). A glassy carbon electrode was used as the working electrode. After coated with O-carboxymethylchitosan modified Fe_3O_4 nanoparticle suspension, the electrode was immersed in a solution of anti-*C. jejuni* monoclonal antibodies 2D12 for immobilization. BSA was applied as a blocker to non-specific binding. Electrodes were incubated in bacteria-contained PBS (pH = 7) buffer at 37.5 °C for 40 min before impedance measurements, which was performed in a solution of $Fe(CN)_6^{3-/4-}$. The regeneration of the antibody immobilized electrode was done by rinsing in glycine–HCl buffer (pH = 2.8) for 20 min, which yielded a RSD of 4.2% for 15 repetitive measurements. The linear range of detection, as R_{ct} vs. logarithm of concentration was used, was 10^3–10^7 cfu/ml ($R^2 = 0.99$). The sensor was stable for 2 months when kept at 4 °C and had 87.8% intensity of signal after 4 months. The specificity was tested with the negative control

Salmonella spp. Besides in PBS buffer, bacteria in patient stool samples were also checked and the response varied in the range of 6 to 7%.

2.2.3. Conductometric biosensors

Conductometric biosensors are based on the modulation of conductance of bio-components placed between a pair of electrodes (Cullen et al., 1990; Gerard et al., 2002; Shah and Wilkins, 2003; Sukeerthi and Contractor, 1994). Because the reciprocal of conductance is resistivity, these sensors are also called chemiresistors (Janata, 2010). Microbial metabolism often brings changes in conductance, capacitance, and impedance, and thus the concepts of conductance, resistance, impedance, and capacitance are considered as different approaches for monitoring and are inter-related in biosensors (Milner et al., 1998; Silley and Forsythe, 1996). Generally, conductometric biosensors include those based on the conductance of a bulk solution, the capacitance at the interface of electrode–electrolyte, and the impedance at the interface (already discussed in above section) (Shah and Wilkins, 2003).

Many papers described the detection of bacteria and biomaterials with conductance based technologies. Sergeyeva developed a conductometric biosensor with the recognition element of phthalocyanine film for detecting peroxidase labeled antibodies (Sergeyeva et al., 1998). Cappelier discussed that the growth of *Campylobacter* species could be observed by monitoring the change in conductance of medium (Cappelier et al., 2000).

Line stated a capacitance based detection method for monitoring the growth of *C. jejuni* (Line and Pearson, 2003). After choosing an optimal broth medium, the metabolism of bacteria was monitored along with a significant change in the capacitance of the solution. The amount of time required for the capacitance to reach a minimum was related to the initial concentration of cells. For example, the longest amount of time (35 h) was related to the lowest concentration (1 cfu/ml) and the shortest amount of time (17 h) was related to the highest concentration (10^4 cfu/ml). Although the results showed high variation among 20 experiments and longer response times compared to other types of biosensors, it showed a possibility of development of the capacitance-based biosensor for analysis of *Campylobacter* spp.

2.3. Mass sensitive biosensors

Mass sensitive biosensors are based on a transduction method involving slight changes in mass of the biosensor. Piezoelectric materials are typically used to analyze the change in mass, as they can be set to vibrate at a specific frequency using an electrical signal. Both the frequency of the electrical signal and mass of the piezoelectric material have an effect on the oscillation of the material, and therefore when chemicals bind to the surface of the sensor, the mass increases and the frequency changes. The change in frequency can be electrically measured, and thus the additional mass can be determined. A biosensor can be fabricated using a piezoelectric material and attaching the recognition element, usually antibodies specific to the pathogen, to the sensor surface. When placed into an environment containing the pathogen, the antibodies facilitate the attachment of the pathogen to the biosensor, which increases the mass of the system, and changes the frequency of oscillation, thereby quickly determining the presence and quantity of the pathogen. There are two types of mass-sensitive techniques: quartz crystal microbalance (QCM), which is also known as bulk wave, and surface acoustic wave. Mass-sensitive techniques are relatively easy to use, cost effective, and offer specificity, sensitivity and direct label-free analysis of pathogens (Velusamy et al., 2010a,b).

C. jejuni has been successfully detected using a QCM biosensor, which is based on lectin-typing. Lectins are proteins or glycoproteins found in plants and animals and are of non-immune origin. They bind specifically to several different types of carbohydrates and their binding properties are typically more stable than those of antibodies. Yakovleva et al. (2011) were able to characterize seven different *C. jejuni* strains using a lectin-typing assay based on a QCM technique using four different commercially available lectins, such as wheat germ agglutinin, with each being specific to different carbohydrates. They immobilized the lectins onto the gold surfaces of the quartz crystals using amine-coupling. Once the bacteria had been attached to the sensor surface and confirmed using atomic force microscopy, the resonant frequency and dissipation responses due to the addition of bacteria were recorded. The significant differences in the dissipation responses for each of the bacterial strains allowed them to discriminately type each strain without any preliminary treatment (Yakovleva et al., 2011).

Similarly, Safina et al. (2008) successfully developed a QCM biosensor for use in flow injection analysis. The biosensor utilized several different lectins, such as Concanavalin A, which were immobilized onto the surface of the quartz crystal electrode. By using several different lectins with selectivity to the carbohydrates present on the cell wall of the bacteria, authors were able to identify and quantify several different strains. In addition, authors showed that a glycine solution at pH 2.5 allowed removing the bound complex on the crystal surface. The sensor was reusable and with a detection limit of 10^3 cells in 30 min (Safina et al., 2008).

Surface acoustic wave (SAW) is a surface sensitive biosensor characterized by two pairs of interdigitated electrodes spaced close to each other, but separated by a piezoelectric substrate, such as quartz. The surface acoustic wave is created by an alternated electric field, which is applied to the transmitter electrode pair producing a periodic surface strain. When the wave and the attached analyte interact, there is a change in the wave velocity and amplitude reflected in frequency shifts. SAW provides an alternative to QCM with higher sensitivity due to its surface sensitive nature (Xu, 2012). While surface acoustic wave devices have been used to detect pathogens, such as *E. coli* (Howe and Harding, 2000), it is not typically used in liquid samples because of the decreased sensitivity due to high energy loss (Xu, 2012).

3. Conclusion

In recent decades, many efforts have been devoted to the rapid and accurate detection of *Campylobacter* spp. by worldwide researchers. Among all of the detection technologies, biosensors have attracted increasing interests, due to their advantages of high sensitivity, high specificity, and real time and non-destructive sensing. Optical, electrochemical, and mass sensitive biosensing techniques have been used to detect these bacteria. The biorecognition elements have included DNA, antibodies, and specific proteins. The target analytes were usually limited to *C. jejuni*. The detection limit was reported to be at least 3 log cfu/ml. Although single cell detection has been hypothesized, no reliable data have been reported to verify this hypothesis. Because *Campylobacter* spp. may cause infectious diseases even at low concentrations, more research is needed in order to obtain biosensing systems with better detection limits and faster response.

Acknowledgments

The authors would like to thank the financial supports from grant USDA-20053439415674A.

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