



Review article

Biosensors for rapid detection of bacterial pathogens in water, food and environment

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ABSTRACT

Conventional techniques (e.g., culture-based method) for bacterial detection typically require a central laboratory and well-trained technicians, which may take several hours or days. However, recent developments within various disciplines of science and engineering have led to a major paradigm shift in how microorganisms can be detected. The analytical sensors which are widely used for medical applications in the literature are being extended for rapid and on-site monitoring of the bacterial pathogens in food, water and the environment. Especially, within the low-resource settings such as low and middle-income countries, due to the advantages of low cost, rapidness and potential for field-testing, their use is indispensable for sustainable development of the regions. Within this context, this paper discusses analytical methods and biosensors which can be used to ensure food safety, water quality and environmental monitoring. In brief, most of our discussion is focused on various rapid sensors including biosensors and microfluidic chips. The analytical performances such as the sensitivity, specificity and usability of these sensors, as well as a brief comparison with the conventional techniques for bacteria detection, form the core part of the discussion. Furthermore, we provide a holistic viewpoint on how future research should focus on exploring the synergy of different sensing technologies by developing an integrated multiplexed, sensitive and accurate sensors that will enable rapid detection for food safety, water and environmental monitoring.

1. Introduction

Various foodborne and waterborne pathogens alongside several airborne environmental contaminants have been the major causes of illnesses in humans and animals (Zeng et al., 2018). Traditionally,

bacteria pathogens are detected via various techniques that rely on growing the pathogens using various differential or selective media (Xuedong and Yuqing, 2015). Even though the traditional techniques of pathogen detection yielded results that led to the successful diagnosis of many pathogenic bacteria in food, water, and the environment, these

Abbreviations: VBNC, Viable but not Culturable; POC, Point of Care; DNA, Deoxyribonucleic Acid; LMIC, Low and Middle-Income Countries; RNA, Ribonucleic Acid; PCR, Polymerase Chain Reaction; LAMP, Loop-Mediated Isothermal Amplification; WHO, World Health Organisation; CFU, Colony Forming Units; US-EPA, United States Environmental Protection Agency; ELISA, Enzyme-Linked Immunosorbent Assay; IMS, Immuno-Magnetic Separation; LOD, Limit of Detection; LOQ, Limit of Quantification; NASBA, Nucleic Acid Sequence-Based Amplification; mRNA, Messenger Ribonucleic Acid; MS, Mass Spectrometry; ESI, Electron Spray Ionization; MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization-Time of Flight; LSPR, Localised Surface Plasmon Resonance; SERS, Surface-Enhanced Raman Scattering; LFIA, Lateral Flow Immunoassay; SELEX, Systematic Evolution of Ligands by Exponential Enrichment; QCM, Quartz Crystal Microbalance; SAW, Surface Acoustic Waves; LOC, Lab-on-a-Chip; ASSURED, Affordability, Sensitivity, Specificity, User-Friendly, Rapid and Robust, Equipment-Free and Deliverable to End-Users; μ PAD, Microfluidic Paper-Based Analytical Devices.

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methods are time-consuming and required about 18–72 h to grow the pathogens to a concentration that can be quantified (Zeng et al., 2018). Also, these traditional techniques have low sensitivity, poor specificity and are laborious and time-consuming to perform analysis. Furthermore, there are some pathogens such as *Vibrio cholerae* and *Helicobacter pylori* which may be present in a food, water or environmental sample in a Viable but not Culturable state (VBNC) thus, they cannot be grown on any routine growth media.

These challenges have led to the demand of a faster technique for the detection of pathogens to ensure the safe health of humans (Ramírez-Castillo et al., 2015; Law et al., 2015). Addressing such needs led to advances in technology starting with the development of the immunological and molecular techniques for detecting bacterial pathogens (Zeng, Wang and Hu, 2018). These techniques were found to be much faster than the traditional culture methods, however, limitations of the antibody cross-reactions often resulted in false-positive results which further led to issues of low sensitivity and poor specificity within the immunological techniques (Dincer et al., 2019; Ramírez-Castillo et al., 2015). On the other hand, the molecular methods are more sensitive compared to the immunological techniques. Nonetheless, these techniques had their inherent loopholes such as those associated with its complex operations and high costs when translated to the point-of-care (POC) formats as it required implementation of challenging analysis steps for instance- the implementation of thermal cycling stage of the amplification process and it is often prone to false hits.

Many of these challenges were previously overcome by laboratories that could afford the cost of highly experienced technicians and equipment but such financial and technical challenges cannot be overcome in many low and middle-income countries (LMIC) (Reboud et al., 2019; Ahrberg, Manz and Chung, 2016). Hence, despite the technical merits of the aforementioned analytical tools, the techniques available for detecting bacterial pathogens remained expensive, less sensitive and these cannot be categorized under the rapid detection tools which are enabled by ever-growing optical and electronic transduction methods (Funari et al., 2018; Formisano et al., 2016). This desire for a highly sensitive, rapid and cost-effective method of detecting bacterial pathogens led to the invention of many rapid analytical sensors in the last decade. These rapid analytical sensors have demonstrated that infectious disease pathogens can be detected economically at a low concentration with fast turnaround times for analysis results. While most of the transduction principles involved within these techniques has been widely applied in medicine for the diagnosis of infectious diseases and drug delivery, little has been done to understand the applications of such sensor technology in the detection of infectious pathogens present in food, water and the environment. Therefore, this paper summarises the rapid analytical sensors which can be used to effectively monitor bacterial pathogens beyond the field of medicine and health and to assess the suitability of these rapid sensors in food safety control, water quality and environmental monitoring.

There are various rapid techniques for detecting microbes in water, food, and the environment such as biosensors and microfluidic sensor techniques (Dincer et al., 2019; Zeng, Wang and Hu, 2018; Ramírez-Castillo et al., 2015). Among all these methods, microfluidic sensors, particularly paper-based microfluidics has gained massive recognition and wider application in clinical diagnostics, food safety, drug delivery, water quality, and environmental monitoring since its invention in 2007 by the Whiteside group (Martinez et al., 2007). The paper-based microfluidic devices are highly specific, selective and sensitive, and its application is highly emphasized in environments where speed, accuracy, ease of operation, and low cost are highly required, and for use in the developing countries where technical and clinical resources are limited thus, encouraging rapid POC testing (Reboud et al., 2019a). The driving force behind this microfluidic device is the nucleic acid technology which makes the rapid detection method very accurate. This is possible because nucleic acids being the parent genetic material are similar in all organisms including plants and animals but differ in

sequence amongst all organisms. Also, nucleic acids which could either be Deoxyribonucleic acid (DNA) or Ribonucleic acid (RNA) are composed of four nucleotide bases so, they are easy to isolate, purify, label and sequence using various nucleic acid sequencing techniques (Zhao et al., 2015; Chang et al., 2013).

In 2000, researchers developed a novel molecular technique to mitigate the shortcomings of the polymerase chain reaction (PCR) technique. This technique which equally utilises the principle of the nucleic acid-based method of identification and operates at a stable temperature for nucleic acid amplification is called the isothermal technique (Notomi, 2000). With the isothermal technique, the detection of pathogens was made easier and cheaper, especially in resource-limited areas (Reboud et al., 2019; Nzelu et al., 2019). Amongst the different isothermal techniques employed in pathogen detection, the loop-mediated isothermal amplification (LAMP) technique has gained widespread popularity amongst the scientific community due to its stability, specificity, and sensitivity. The LAMP technique involves a very peculiar process, it uses six specific primers in the first stage and four primers during the amplification, elongation, and recycling steps (Alonso-Padilla et al., 2019).

Despite its widespread application, the LAMP technique encounters some limitations during usage (Motamedi et al., 2011). The extraction, amplification, and identification of microbial DNA in various water, food, and environmental samples is quite difficult, especially when the pathogens are present in a low amount. This results in a lower amount of the target nucleic acids which then requires laborious extraction and amplification. Therefore, the addition of paper-based analytical devices to the LAMP technique after its emergence in 2007 was used to overcome the limitations associated with the LAMP technique (Gong and Sinton, 2017). The risk of biocontamination of samples is reduced in the paper-based analytical devices due to the low sample size required for assay, the typical sample volume ranges from 0.1 to 100 μL (Mao et al., 2020). Another exciting feature of the incorporation of paper-based analytical devices is that successful amplification of pathogenic nucleic acid can be detected visually through the naked eyes, or cell phones amongst other methods (Reboud et al., 2019; Hui et al., 2018).

According to the World Health Organisation (WHO), foodborne infections remain one of the major causes of illness in the world. (Franz et al., 2019). For instance, in the United States, more than 45 million people suffer from foodborne illness with over 120,000 hospitalisations, 3,000 deaths and \$15 billion economic loss annually (Ali et al., 2020). Thus, it is vital to conduct a rapid routine test for the presence of pathogens in any food sample before consumption. For a food sample to be microbiologically satisfactory for consumption, the following conditions specified by the Centre for Food Control must be met; *Campylobacter* spp, *Shigella* spp, *E. coli* (including O157:H7), *Salmonella* spp and *V. cholera* must not be detectable in 25 CFU mL^{-1} of that food sample while *V. parahaemolyticus* and *S. aureus* must not be detectable in 20 CFU mL^{-1} of the food sample. Also, *C. perfringens* must not be detectable in 10 CFU mL^{-1} while *B. cereus* must not be detectable in 1000 CFU g^{-1} . Also, no bacteria must be detected in 10 CFU g^{-1} of ready-to-eat food (Chua et al., 2014). This strongly indicates that any analytical sensor used for food analysis must have promising sensitivity (<10 CFU mL^{-1}). Similarly, the acceptable limit of *E. coli* in freshwater suitable for recreational purposes is 30–110 CFU/100 mL while that of *Enterococci* in marine water for recreation is 100–320 CFU mL^{-1} (US EPA, 2012). Following these guidelines, rapid analytical sensors are suitable for detecting bacterial pathogens present in environmental water (Table 2).

In this paper, the concept of bacterial detection is introduced, the previous and current methods of bacterial identification are briefly discussed. In the second section, the different culture-based techniques for microbial pathogen detection are briefly discussed. The third section ushers in the various rapid methods for detecting microbial pathogens in water, food, and the environment. Many reports abound on the application of the rapid sensor techniques for detecting microbial pathogens

in medicine however, our review only focused on the suitability of rapid biosensors in monitoring pathogens present in food, water and the environment. Finally, we proposed possible insights for future research in the field of rapid diagnostics.

2. Conventional methods for pathogen detection

Since its discovery in the 1660s, the detection of microorganisms has been carried out using culture-based means of identification (Ruoss and Wynn, 2019). These methods were dependent upon the unique biological and chemical features of the pathogens and their ability to be cultivated in an artificial environment (Ray et al., 2017). These methods include serology, biochemical tests and the more recent molecular methods to provide the evidence necessary for understanding the relationship between diseases and their causative agents (Fang and Ramasamy, 2015). This detection method for pathogens relied majorly on the presence or absence of certain distinctive physical features of the pathogens. However, the techniques are only suitable for those pathogens that are culturable. Therefore, our understanding of the diversity and physiology of microbial communities was limited to just about 1% of the entire microbial community (Martiny, 2019). Table 1 shows the sensitivities and turnaround time of the conventional techniques used for the detection of bacterial pathogens in different sample matrices. while Fig. 1 shows the setup of the different culture-based techniques for microbial detection. Based on their limits of detection, the culture techniques are not suitable for the rapid diagnosis of pathogens in food, water and the environment.

2.1. Microbial culture

The microbial culture technique is regarded as “the gold standard” and it provides a model for the *in-vivo* and *in-vitro* examination of the microbial pathogens thereby, enhancing the understanding of microbial diversity and the diseases caused by each pathogen. In addition, it enables the study of bacterial susceptibility to antibiotics which is vital for the recommendation of specific treatments (Lagier et al., 2015). Generally, the typical detectable range of pathogens using culture media is about 2.5×10^3 – 10^3 CFU ml⁻¹ (Gill, 2017; Bargellini et al., 2011). However, the culture technique of microbial isolation and identification has faced some limitations. For instance, the process is time-consuming, requiring about 1–2 days for bacteria growth to occur, and the process requires expensive human resources and instruments thus, it is

inadequate where a rapid result is demanded. (Hai et al., 2019; Lagier et al., 2015).

2.2. Biochemical and immunological test

The biochemical test is one of the most useful conventional techniques for detecting bacterial pathogens and it is usually performed after bacteria culture thus, its limit of detection is between 10^4 CFUml⁻¹ and 14×10^6 cells/100 ml (Chauhan et al., 2017; Gill, 2017). The underlying principle of biochemical tests is based on the differences in the biochemical activities of bacteria (Rodrigues et al., 2017) such as the ability to hydrolyse starch amongst others (Hameed et al., 2018). The biochemical test has aided scientists and researchers in the identification and classification of bacterial strains from food, water and the environment. However, the technique has shown some limitations (Granada, 2019; Ochoa-Díaz, Daza-Giovanetty and Gómez-Camargo, 2018). For instance, some tests are not specific and rely on a series of other biochemical tests to identify pathogens that fit the test profiles (Ogunware et al., 2020). It is also less accurate, and researchers have just recently begun reporting limitations in the accuracy of the biochemical tests. For example, the *E. coli* which is positive to methyl red and has even been used as a conventional positive control for the methyl red test has been reported as being negative in a recent study to determine the antibacterial activity of pigments from soil organisms (Qayyum et al., 2020). Also, some emerging food-borne zoonotic pathogens such as *Arcobacter* are biochemically inert hence, they cannot be identified using biochemical tests (Ramees et al., 2017). Therefore, the biochemical technique of identifying microbial pathogens in food, water and environment is unreliable and unspecific.

The immunological identification technique is based on the principle of specific binding between antibodies and antigens (Chang et al., 2016). The most widely used immunological techniques for the detection of microbial pathogens include the enzyme-linked immunosorbent assay (ELISA) and immuno-magnetic separation (IMS) (Välilä et al., 2015). The basic requirement for the immunological technique is the availability of known and appropriate antisera containing monoclonal or polyclonal antibodies that can detect the presence of an unknown antigen or microbial pathogen. Generally, the LOD of immunological assay techniques is between 10^4 and 10^5 CFU ml⁻¹ giving it the advantage of higher sensitivity relative to other previous techniques (Zhao et al., 2020). Although the immunological techniques can be used to analyse food, water and environmental samples faster, cultural enrichment is

Table 1
Summary of conventional techniques used for the detection of bacterial pathogens in food, water and environment.

Techniques	Bacterial pathogens	Sample matrix	LOD	Time	References
Bacterial culture	<i>C. jejuni</i>	Meat, Poultry	10^6 CFUml ⁻¹	48 h	(Buss et al., 2019;
	<i>L. pneumophila</i>	Hot water samples	2.5×10^3 CFUml ⁻¹	>24 h	(Gill, 2017) Bargellini et al., 2011) (Tilton et al., 2019)
	<i>E. coli</i>	Wash water	8×10^8 CFUml ⁻¹	16 h	
Metagenomics	<i>E. coli</i> O157:H7	Irrigation water	10^3 CFUml ⁻¹	24 h	(Maguire et al., 2021)
Biochemical tests	<i>P. aeruginosa</i>	Rice and Eggs	10^4 CFUml ⁻¹	N.D	(Hinić et al., 2017)
	<i>E. coli</i>	Drinking water	14×10^6 cells/100 ml	>1h	(Chauhan et al., 2017)
ELISA	<i>L. monocytogenes</i>	Lentil Salad	5.4×10^3 CFUml ⁻¹	N.D	(Zhang et al., 2016a;
	<i>E. coli</i> O157: H7	Drinking water	1×10^3 CFUml ⁻¹	< 3 h	(Zhang et al., 2016)
	<i>Litopenaeus vannamei</i>	Aquatic water	10^4 CFUml ⁻¹	1 h	(Su et al., 2016)
IMS	<i>S. typhimurium</i>	Fruits and Vegetables	10^2 CFUml ⁻¹	30 mins,	(Srisa-Art et al., 2018)(Lun et al., 2018)
	<i>V. parahaemolytica</i>	Environmental water	10^1 CFUml ⁻¹	4–5 h	
NASBA	<i>Salmonella spp</i>	Fruits and Vegetables	7×10^{-1} CFUml ⁻¹	12 h	(Zhai et al., 2019)
LAMP	<i>E. coli</i>	Treated tap water	1viable cell/100 ml	3–4 h	(Heijnen and Medema, 2009)
	<i>Salmonella spp</i>	Milk, pork and beef samples	6.7 CFUml ⁻¹	40 mins	(Mei et al., 2019)
	<i>E. faecalis</i>	Fresh and marine water samples	10 CFUml ⁻¹	1 h	(Lee et al., 2019)
PCR	<i>E. coli</i> O157:H7	Soil and environmental samples	2.6×10^4 CFUg ⁻¹ – 3.5×10^3 CFUml ⁻¹	<16 h	(Ibekwe and Grieve, 2003)

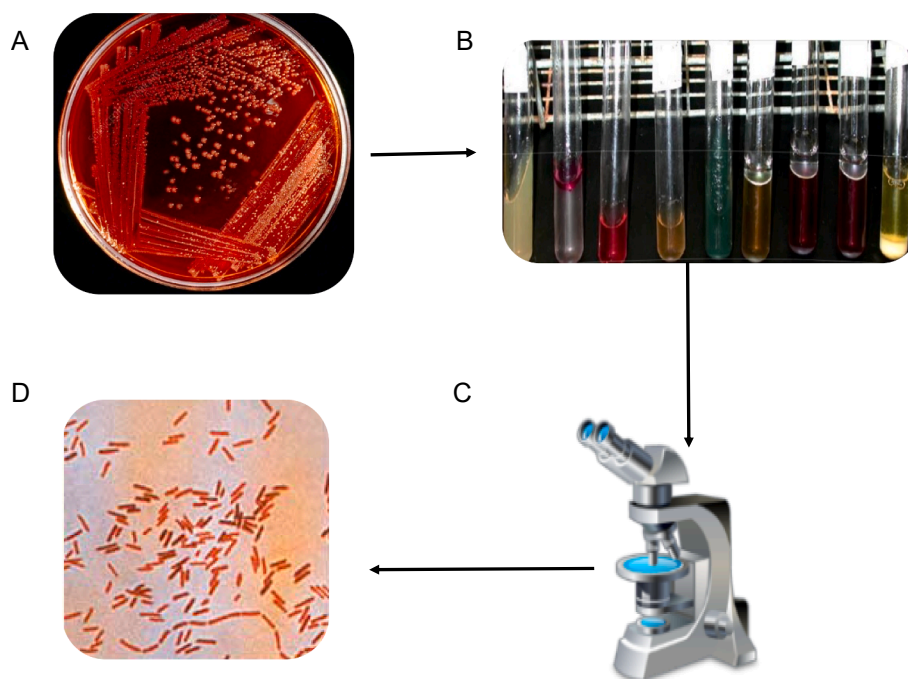
ND = Not detected;

Table 2

Summary of rapid sensor techniques used for the detection of bacterial pathogens in food, water and environment.

Detection techniques	Bacterial pathogens	Sample matrix	LOD	Time	References
Electrochemical biosensors	<i>Salmonella typhimurium</i>	Fresh Vegetables	10^1 CFUml ⁻¹	60 mins	(Muniandy et al., 2019)
	<i>E. coli</i> O157: H7	Drinking water	10^2 CFUml ⁻¹	30 mins	(Brosel-Oliu et al., 2018)
Mass-sensitive biosensors	<i>E. coli</i> O157:H7	wastewater	3 CFU/100 ml	2 h	(Jayamohan et al., 2015)
	<i>E. coli</i>	Meat Products	1 CFUml ⁻¹	140 mins	(Li et al., 2018)
	<i>E. coli</i>	Water samples	2 CFUml ⁻¹	2 mins	(Gupta et al., 2019)
	<i>P. aeruginosa</i>	Tap and grey water	500–1000 CFUml ⁻¹	20 min	(Mondal et al., 2020)
Immunoassay	<i>Salmonella enteritidis</i>	Milk and cheese	1CFUml ⁻¹	40 mins	(Zeinhom et al., 2018)
					(Mutreja et al., 2016)
Lateral Flow Immunoassay	<i>S. typhimurium</i>	Drinking water	10CFUml ⁻¹	N.D	
	<i>E. coli</i> O157:H7	Tap and lake water	3.8 CFUml ⁻¹	10mins	(Pandey et al., 2017)
	<i>V. mimicus</i> and <i>Vibrio spp</i>	Freshwater fish and shellfish	5×10^5 – 10^6 CFUml ⁻¹	15 mins	(Wang and Salazar, 2016)
	<i>E. coli</i> O157:H7	Water samples	133 CFUml ⁻¹	3 h	(Hassan et al., 2019)
Aptamer-based assay	<i>Salmonella typhimurium</i>	River water			
		Apple juice	6 CFUml ⁻¹	<30 mins	(Bagheryan et al., 2016)
μPADs	<i>P. aeruginosa</i>	Drinking water	60 CFUml ⁻¹	30 mins	(Das et al., 2019)
	<i>E. coli</i>	Tap water	2.9×10^2 CFUml ⁻¹	30 mins	(Brosel-Oliu et al., 2018)
	<i>Salmonella typhimurium</i>	Milk	33 CFUml ⁻¹	2 h	(Hou et al., 2019)
	<i>E. coli</i>	Drinking water	50 CFUml ⁻¹	8 mins	(Altintas et al., 2018)
	<i>E. coli</i>	Field water samples	10 CFUml ⁻¹	90 secs	(Park and Yoon, 2015)

N.D = Not detected.

**Fig. 1.** Schematics of culture-based techniques for detection of bacterial pathogens. Adapted from (Wang and Salazar, 2016). (A) Isolation of microorganisms using a growth medium. (B) Biochemical test reaction on isolated microorganisms. (C) Microscopical examination of isolates. (D) Stained microbial cells on a microscopical slide.

still required for the assay and this enrichment is often considered as the major limitation because the process of culture takes time (Valderrama et al., 2016).

2.2.1. Enzyme-linked immunosorbent assays (ELISA)

In ELISA, an unknown bacteria antigen is detected using a known antibody that has been linked to an enzyme when the antibody and antigen bind together. A successful binding will lead to the production of a visible colour change (Välimaa et al., 2015). An important element that affects ELISA is the specificity of the antibody in use. The antibody in use could affect the reaction process and may result in low specificity and sensitivity thus, giving rise to false-positive results. To prevent this, ELISA is often combined with other detection techniques (Hameed et al.,

2018) and some scientists have investigated the non-specificity of ELISA to eliminate the false negative and positive results attributed to the process (Waritani et al., 2017).

Gehring et al evaluated the specificity, sensitivity and reproducibility of the ELISA technique. They evaluated two ELISA kits for their effectiveness in the detection and differentiation of Shiga toxin 1 and Shiga toxin 2 produced by Shiga toxin-producing *E. coli* from food and water samples (Gehring et al., 2017). ELISA has a high limit of detection however, researchers overcame this challenge through cultural enrichment. To develop a more sensitive method and overcome the challenges associated with the limits of detection, Guo and his team developed a novel ELISA for the detection of microbial pathogens in milk using a DNA-based Hybridisation Chain Reaction. This novel method had a LOD

that was 185 times more sensitive than the conventional ELISA technique which has a LOD of 10^3 CFU ml⁻¹ (Guo et al., 2016a; (Wang and Salazar, 2016).

2.2.2. Immunomagnetic separation (IMS)

The Immunomagnetic Separation (IMS) technique utilizes immunomagnetic beads to detect pathogens from samples. This technique is similar with ELISA however, the assay selectively concentrates the target pathogen by allowing it to grow while suppressing the growth of other non-target pathogens. The target concentration is done using a 'magnetic bead' that is conjugated with the antibodies against the target pathogens (Hussain et al., 2017; Jones, 2015). The IMS technique gained wide application due to this ability to exclusively separate and concentrate the target pathogen from various samples within a short period. Currently, the IMS technique is used in combination with other techniques such as PCR to increase the sensitivity of the assay. The combination of IMS with other assay techniques is necessary because it shortens the time required to detect bacterial pathogens. (Dąbrowiecki et al., 2019) developed a system that reduced the time required to detect *Legionella pneumophila* in water samples from the conventional 14 days to just a few hours by combining IMS with flow cytometry. The combination of IMS with other techniques eliminates the possibility of false-positive and negative results thereby increasing the sensitivity and throughput of the technique.

Generally, immunological assays typically can produce the same accuracy over different detections. They are less complicated and very easy to use given that it has a yes/no or present/absent result for the user to observe. Additionally, it is relatively accurate since the test incorporates a control region which ensures that the results are accurate (Ong et al., 2021).

2.3. Molecular methods for pathogen detection

The molecular technique of detecting microbial pathogens in food, water and environment is relatively more sensitive and specific compared to other culture-based techniques such as immunological and biochemical tests because these methods involve the detection and quantification of pathogens by targeting and amplifying specific portions of the pathogen's genetic material. The need for the molecular technique was necessitated because of the arduous procedure involved in the isolation and identification of the target microbial pathogen from the pool of other microbes present in food, water and environment using conventional culture-dependent techniques. Many of these pathogens may be present in quantities low enough to be detected using the culture-based technique, but high enough to illicit infections (Ramírez-Castillo et al., 2015). Interestingly, the molecular technique can accurately identify microbial pathogens up to the species level (Sáez et al., 2017).

2.3.1. Polymerase Chain reaction

With the PCR technique, few copies of nucleic acid (DNA or RNA) that are present in a sample can be amplified to generate billions of copies (Bouchez et al., 2016). This is done through a series of thermal cycling steps using the polymerase enzyme. The process involves the denaturation of the double-stranded DNA molecules at high temperatures. Afterward, specific primers anneal to complementary DNA strands and the complex is extended by the polymerase enzyme. The amplified PCR product can be seen as bands after staining with ethidium bromide on electrophoresis gel (Maurye et al., 2017). Despite being common, this technique had to be validated and standardised to increase its sensitivity, reduce the cost, time and the various analytical steps involved in the assay process (López et al., 2017).

Among PCR techniques, real-time PCR is the most preferred. The real-time PCR continuously monitors the process of the target DNA amplification in real-time rather than at the end of the reaction and it amplifies particular fragments of DNA molecules present in a sample.

Hence, the different amounts of pathogens and species present in a sample can be ascertained using PCR (Bouchez et al., 2016). This is done by measuring the intensity of the fluorescent signal produced by intercalating dyes (Law et al., 2015). The commonly used fluorescent signal system is SYBR green (Bintvihok et al., 2016). Tyagi et al developed a sensitive and highly reproducible SYBR green-based real-time PCR that can detect tdh-positive pathogenic *Vibrio parahaemolyticus* from crude lysate from iced shrimp and with a LOD at 10^1 CFU ml⁻¹– 10^6 CFU ml⁻¹ (Tyagi et al., 2009).

Most PCR procedures are carried out using available commercial kits such as TaKaRa Genomic DNA extraction kit (Liu et al., 2019), QIAmp DSP DNA mini kit (Allard et al., 2019) and KAPA HiFi HotStart ReadyMix (Pereira et al., 2017). However, the high cost of these kits makes its application very limited (Hønsvall and Robertson, 2017a). Also, certain conditions such as the nature of the target sequence and enzyme activity can prevent primers from annealing to targets and limit the PCR amplification efficiency (Cunha, 2019). When compared to other culture-dependent techniques, PCR does not distinguish between viable and non-viable pathogens (Wolffs et al., 2017). As a result, DNA fragments from dead microbial pathogens could also be amplified during the PCR process. Also, the technique must be carried out on-site in a well-equipped laboratory and by a trained technician. Furthermore, the process requires the addition of gel electrophoresis for the identification of the target DNA thus, making it techno-economically unsuitable in areas with limited financial and technical resources.

2.3.2. Isothermal amplification

2.3.2.1. Loop-Mediated isothermal amplification. LAMP is a comparatively novel and cheap method that can rapidly amplify nucleic acids with higher specificity and sensitivity. LAMP operates under an isothermal state using Bst DNA polymerase with large strand fragment and four uniquely designed primers (2 inner and 2 outer) that recognises six discrete regions of the target DNA (Lin et al., 2020; Li et al., 2017). Fig. 2 shows the principle of LAMP technology. LAMP has various benefits compared to the conventional PCR technique. For instance, PCR requires about 2 h to complete the thermal cycling phase whereas LAMP operates under isothermal conditions and requires about 59°C to 65°C and therefore any conventional heating system such as a water bath which can sustain the temperature for 1 h is enough for a complete cycle, producing about 1000-fold amplification products (Mao et al., 2020; (Lin et al., 2020).

A group of researchers has recently developed a simple and cost-effective LAMP assay that could detect microbial pathogens from food, water and environment, particularly in resource-limited regions. The assay consists of an isothermal control implemented by a home-built Peltier heating device that can visually detect *Bacillus cereus*, *Escherichia coli*, *Salmonella enterica*, *Vibrio fluvialis* and *Vibrio parahaemolyticus* in 1 h with a LOD of 7.2 copies/μL genomic DNA and 100% efficiency (Xia et al., 2016). However, despite the significance of LAMP in the detection of pathogens, one major limitation is that LAMP is very susceptible to contamination which can lead to false-positive results (Mao et al., 2020; Li et al., 2017).

Although PCR and isothermal amplification play a role in the detection of pathogenic bacteria, they have certain features which distinguish them from each other. Isothermal amplification, particularly LAMP is an emerging technique while PCR is an older detection technique. LAMP eliminates the need for multiple temperature cycling, unlike PCR which is highly dependent on the multiple temperature cycles. LAMP assay can be performed at relatively low temperature, typically around 60°C to 65°C while a higher range of temperature of up to 95°C is required for the PCR process (Lin et al., 2020). LAMP requires low manpower, training and reagents, while PCR typically requires advanced training, laboratory setting, very expensive reagents and instruments (Picot et al., 2020).

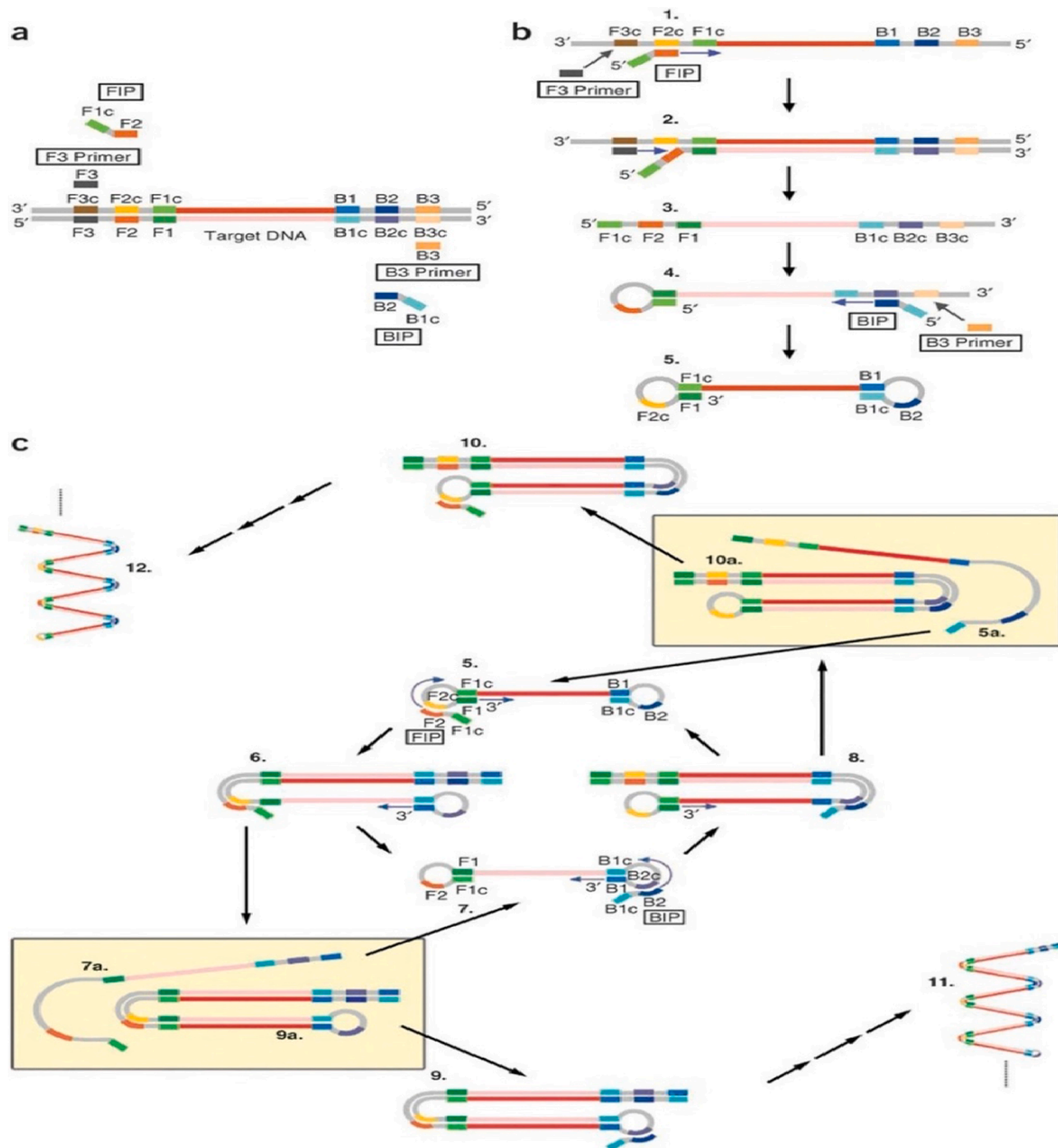


Fig. 2. Principle of LAMP and uses four specific primers to recognise six discrete regions of the target DNA. Genetic amplification and detection are achieved at a constant temperature and in one step including incubation of samples, primers and polymerase enzyme. reprinted with permission from (Tomita et al., 2008).

2.3.2.2. Nucleic acid Sequence-Based amplification (NASBA). NASBA is an RNA-based technology used for the selective detection of viable microbial pathogens. It emerged as an alternative to PCR because the conventional PCR technology uses thermal cycling and extension to achieve DNA amplification of more than a million-fold within 4 h. However, NASBA is an alternative method used to amplify RNA up to a billion-fold within 2 h at a constant temperature (Lin et al., 2020). NASBA does not require specialized thermocycling equipment because the reaction process occurs at about 41°C – 55°C. Additionally, RNA amplification with PCR is achievable using a reverse transcriptase enzyme that can synthesize a DNA strand complementary to the template strand. The conventional PCR amplification technique requires about 20–25 cycles to generate significant products however, NASBA requires just about fewer cycles to generate the same number of amplicons thus, making NASBA a more rapid technique (Hønsvall and

Robertson, 2017a).

NASBA has been proven to be a sensitive and effective method in the detection of *Salmonella* species (Lin et al., 2020). NASBA was applied in a study to develop a rapid, specific, sensitive and effective detection of *salmonella* from food of animal origin. In this study, 48 *salmonella* and 18 non-*salmonella* strains from pork, beef and milk matrices were examined and the assay demonstrated the ability to detect viable cells with high specificity and LOD of 7×10^{-1} CFUml⁻¹ after 12 h of pre-enrichment. (Zhai et al., 2019). The assay, However, the pre-enrichment step makes the assay process less rapid hence, unsuitable for use where rapid response is required. Generally, NASBA exclusively amplifies mRNA targets, and mRNA can only be produced by metabolically active cells thus, making it a good molecular marker for detecting viable microbial pathogens. However, there have been reports of amplification of mRNA even from inactivated and dead microbial pathogens (Hønsvall and

Robertson, 2017a,b; Ju, Moyne and Marco, 2016). Therefore, there is a need to ensure that amplified mRNA targets are from viable microbial cells and one way to address this is by detecting viability marker genes in microbial pathogens. For instance, mRNA viability markers such as β -tubulin (Hønsvall and Robertson, 2017b) and EF-Tu mRNAs (Ramezani et al., 2019) have been developed for amplification of viable microbial nucleic acid.

2.4. Metagenomics

Metagenomic approaches are attracting increasing attention in recent times, in the study of microbial community composition and function (Alves et al., 2018; Stefanini and Cavalieri, 2018). Metagenomics refers to the study of genetic materials recovered from different environmental samples such as water, human faces, etc (Acharya et al., 2020). Generally, the traditional molecular identification technique involves obtaining a sample, culturing and sequencing any observed microbial growth. While this method, especially the PCR approach has proven to be successful in the identification of many disease-causing pathogens, current technology now permits extraction of the nucleic acids directly from a sample to reveal all the information regarding the entire microbial community, without culturing the sample (Forbes et al., 2017).

Basically, there are two types of metagenomics currently employed in the detection of microbes: the targeted sequencing and the metagenomic shotgun sequencing. Currently, the two metagenomic approaches are very popular in identifying the microbial community in an environment, but only the metagenomic shotgun sequencing can shed light on their functionality in that environment (Forbes et al., 2017; Pérez-Cobas et al., 2020). In targeted metagenomics, particular regions of microbial genome that are conserved including 16 s rRNA and 18 s rRNA that are conserved are amplified with PCR primers and then sequenced. The nature of these conserved regions permits the amplification of particular groups of organisms (Mitreva, 2017). However, major limitations of this technique are that it is nearly impossible to directly determine the microbial community functionality from generated data, and the inability to identify microbes to the species level (Xu

and Zhao, 2018). On the other hand, the metagenomic shotgun approach gives information regarding the microbial community composition as well as their functionality, thus giving the knowledge of what organisms are present and the roles they are playing in that environment (Pérez-Cobas et al., 2020; Sharpston, 2014). Hence, this approach enables researchers to identify the type and number of microbial populations present in any sample down to the species level, while being able to completely sequence various parts of the organism's genome.

2.5. Mass spectrometry

Mass spectrometry (MS) is an analytical technique used for the measurement of the mass-to-charge ratio of molecular ions using an instrument called a mass spectrometer (Singhal et al., 2015). In the MS technique, a sample is ionised by colliding it with a beam of electrons which leads to the break-up of some of the sample's molecules into either fragmented or non-fragmented positively charged molecules (Nicolescu, 2017). A separation of the ions occurs based on their mass and charge either by subjecting the (fragmented) ions to an electric or magnetic field. During this process, similar mass-to-charge ions will be deflected equally and this deflecting is detected using an instrument such as an electron multiplier (Nmr, 2002). The results are usually displayed as spectra whose intensity depends on the mass-to-charge ratio (Nicolescu, 2017). MS was invented towards the end of the 20th century, but the integration of electron spray ionization (ESI) and matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) has revolutionized the technique (Everley et al., 2008). Fig. 3 shows the operational principle of MALDI-TOF in the detection of bacterial pathogens. MALDI-TOF is preferable over ESI because of its high speed, throughput and automation (Singhal et al., 2015). The MALDI-TOF technique has shown greater speed and accuracy than the conventional technique for detecting pathogens (Haigh et al., 2013). Guembe et al., (2014) demonstrated a MALDI-TOF MS that performed better than the conventional culture technique of microbial detection.

In the study, MALDI-TOF spectrometry was used to detect colonising pathogens in blood culture and catheter-related bloodstream infections

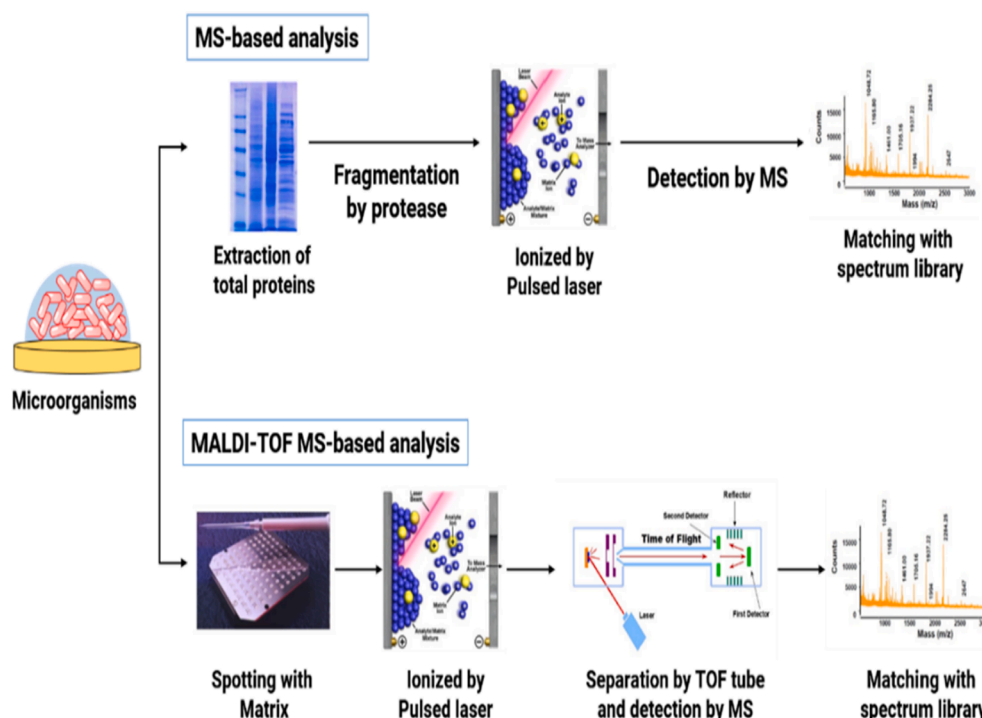


Fig. 3. Principle of microbial detection using MALDI-TOF technology (Han et al., 2021).

from intravascular catheter tips. The result showed a sensitivity and specificity of 69.0%/66.7% and 84.7%/75.2% respectively. Although the technique proved to be a greater diagnostic approach for the detection of catheter-related bloodstream infections, however, the challenges encountered rendered the results nearly approximate. For instance, MALDI-TOF was able to detect about 62.5% of yeast (*C. albican*) and 40 % of bacteria (*S. aureus*) bloodstream pathogens. Additionally, the long period of time involved in the pre-analytical stage equally made the technique less efficient (Guembe et al., 2014).

MALDI-TOF MS has equally shown a great promise in the identification of pathogens in food, water and the environment. For instance, MALDI-TOF has been applied in the detection of pathogens in milk, yoghurt and pork (Nicolaou et al., 2012; Angelakis et al., 2011). A team of researchers was able to identify microbes from the environment using the taxon-specific phenotypic properties. Furthermore, they were able to group the microbes belonging to different taxa into aerobic and halophilic microbes (Munoz et al., 2011).

In MALDI-TOF, thermal desorption of ribosomal proteins of bacterial pathogens in the matrix with analytes occurs due to laser impacts. Ions in the electric field are accelerated and they begin to move at a speed equivalent to their mass and electric charge. The path of movement permits additional separation which results in differences in the time-of-flight of the desorbed proteins such that the mass of the protein can be calculated after being detected on the top of the vacuum tube (Han et al., 2021).

3. Biosensors for pathogen detection

Pathogens are responsible for various infectious diseases and death globally. These infectious diseases are preventable if the causative pathogens are accurately and rapidly detected (Mao et al., 2020). Therefore, the techniques used for their detection should be rapid, reliable, specific and cheap to make it available especially in resource-limited areas (Hameed et al., 2018). The detection of bacterial pathogens from food, water and environment can be achieved by using either conventional or biosensor techniques. Although the conventional or culture-based technique have been classified as the “gold standard” for detecting bacterial pathogens, these techniques had the advantage of being able to detect only viable bacterial isolates that can be studied and characterised further (Paul et al., 2019). However, the technique is labor-intensive, time-consuming, less specific and sensitive and thus, ineffective. On the other hand, the use of biosensors offers greater benefits compared to conventional techniques in the detection of bacterial pathogens from food, water and the environment because the technique is rapid, very sensitive, specific, selective, less laborious and very effective (Paul et al., 2019).

There has been a recent increase in public health awareness and safety which has led to an increase in the demand for rapid sensors in food safety control and water quality monitoring. There is a prediction that there will be a rise in the global analytical sensor (biosensor) market from \$19.2b in 2019 to \$31.5b by 2024 (Chocarro-Ruiz et al., 2017).

Biosensors are analytical devices that consist of two components, a biological element such as nucleic acids, antibodies, cells and enzymes (that interacts with the target analyte) and a physiochemical transducer that transforms the result of the interaction into an optical, piezo-electrical, or electrochemical signal (Hameed et al., 2018). The biorecognition elements in biosensors utilize the lock-and-key principle of enzyme-complex in the recognition of analytes present in a sample. When compared to other bacteria detection techniques, biosensors are more rapid, specific, sensitive and very reliable. The main consideration when fabricating biosensors is to manufacture a reusable, sensitive and specific device that is independent of environmental factors such as temperature and pH (Mehrotra, 2016).

One major challenge of biosensors is the cost of commercializing the devices for food safety and water quality because of the high cost of the products which makes its wide application very limited. Biosensors are

not heat resistant because they contain some heat-sensitive molecules such as enzymes therefore, they cannot be sterilized using heat. Aside from the challenge of stability and commercialization, the high cost of research and development in the field of biosensors makes adoption of the technology quite difficult (Chocarro-Ruiz et al., 2017).

Two vital parameters are used to explain the sensitivity of biosensors and they include the limit of quantification (LOQ) and limit of detection (LOD). The LOD of a rapid sensor is an indication of the minimum concentration of pathogens/cells that can be detected using that sensor while the LOQ is the minimum concentration of pathogens/cells that be accurately and consistently detected and measured. Although both are very important parameters, however, researchers have adopted the LOD as a standard measure of analytical sensitivity (Forootan et al., 2017).

Despite being faster and more reliable means of detecting bacterial pathogens, the sensitivity of analytical sensors varies from one sensor to the other. These differences in the sensitivities could be due to the nature of the sample matrices analysed. For instance, it is faster to conduct a bacterial analysis of liquids than that of solid because the liquid contains a more homogeneous mixture of pathogens than solids. Therefore, the sensitivity of analytical sensors must be validated to a large extent by using sample preparation when analysing solid food samples. However, such sample preparation will involve culturing the bacteria before analysis which will then invalidate the rapidity of the assay hence, a sample preparation step that does not entail bacterial culture such as using miniaturizing machines is necessary to truly determine the sensitivity of these biosensors.

There are various rapid sensors employed in the detection of pathogens however, the commonest rapid sensors include biosensors and microfluidic sensors (Li et al., 2019). These common rapid analytical sensors used for detecting bacterial pathogens including their sensitivities and assay time are summarized in Table 2, while the differences between conventional techniques and biosensors are summarized in Table 3. These emerging rapid sensors have very high sensitivity and specificity, so they can be used to directly detect even very low levels of bacterial pathogens without enrichment. These rapid sensors have shown the ability to achieve high portability, miniaturization and they permit the incorporation of digital technologies such as smartphones and are very relevant in low-resource settings (Poghossian et al., 2019). Thus, enabling non-experts and technicians to easily apply them, especially in LMIC with a high infectious disease burden (Kruk et al., 2018). Various categories of biosensors have been applied in the detection of bacterial pathogens and they are summarised below (Mehrotra, 2016).

3.1. Optical biosensors

Optical biosensors convert the result of the interaction between the biorecognition agents and analytes into an optical signal that is directly proportional to the concentration of the analyte (Wang and Salazar, 2016). Optical biosensors can either be label-free whereby signal transduction is produced due to the interaction between the transducer and analyte or label-based whereby a label is used and the optical signal transduction is produced by fluorescent or colourimetric method (Pinto et al., 2018). However, the use of a label-based approach is limited by the fact that the successful interaction between the transducer and analyte may be altered thereby giving off erroneous results (Damborský et al., 2016). Optical biosensors are the most widely used biosensors in the detection of microbial pathogens in food (Khansili et al., 2018), water (Bhardwaj et al., 2019; Ferrero Martin et al., 2016) and the environment (Gupta et al., 2017). Their mechanism of action is based on techniques such as light absorbance, light polarization and surface plasma resonance (Khansili et al., 2018). Immunosensors are the most widely used optical sensors, especially the lateral flow immunoassay and aptamer-based immunoassay.

Optical biosensors signal transduction is produced by fluorescence, localised surface plasmon resonance (LSPR), Surface-enhanced Raman Scattering (SERS) or colourimetric method (Pinto et al., 2018). Due to its

Table 3

Summary of the key variations between conventional and biosensor techniques used for the detection of bacterial pathogens in food, water and environment.

Detection technique	Principle of detection	Limit of detection	Merits	Drawbacks	References
Electrochemical biosensors	Measurement of target analyte based on variations in resistance, conductance and/or capacitance	10^1 CFUml ⁻¹ – 10^2 CFUml ⁻¹	- Allows on-the-site assay Can use very small volume of analyte. Easy miniaturization, and very low limits of detection	- May interact in a non-specific manner with targets in a complex sample matrix, resulting in the transduction of false signals.	(Muniandy et al., 2019) (Brosel-Oliu et al., 2018) (Choudhary and Arora, 2022)
Mass-sensitive biosensors	Measurement of the mass difference per unit area by determining the variation in frequency of a quartz crystal resonator	3 CFU/100 ml	- Very cost-effective, label-free and generally suitable for rapid detection of the analyte in portable formats	- Performance is affected by external factors such as temperature Limited to lab-based measurement due to their large size	(Li et al., 2018) (Gupta et al., 2019) (Alassi et al., 2017) (Parsajoo et al., 2012)
Immunoassay	Binding of specific antibody to a specific antigen	1 CFUml ⁻¹ – 2 CFUml ⁻¹	- Provides very fast, sensitive and specific detection Lower limits of detection	- Could lead to cross-reactivity due to binding of antibodies to the structural analogue of analytes	(Zeinhom et al., 2018) (Mutreja et al., 2016) (Sotnikov et al., 2021)
Aptamer-based assay	Binding of short nucleotide fragments to multiple target analytes	6 CFUml ⁻¹ – 2.9×10^2 CFUml ⁻¹	- Permits portability, automation and miniaturization Offers lower limits of detection	- High flexibility of aptamers could result to poor affinity to targets	(Das et al., 2019) (Brosel-Oliu et al., 2018) (S. Zhang et al., 2021)
μPADs	Manipulation of tiny amounts of fluids through wicking	10 CFUml ⁻¹ – 50 CFUml ⁻¹	- Very portable, highly specific, sensitive, selective and permits high-end technological integration such as cell phones	- Sensitivity is dependent on sample matrix Accuracy could be affected by instability of reagents	(Hou et al., 2019) (Altintas et al., 2018) (Park and Yoon, 2015)
Bacterial culture	Identification of bacterial based on growth characteristics	10^6 CFUml ⁻¹ – 8×10^8 CFUml ⁻¹	- Permits only living cells to grow The process is relatively cheaper	- Highly prone to cross-contamination Time and labour-intensive	(Buss et al., 2019; (Gill, 2017) Gill, (2017) Bargellini et al., 2011) (Tilton et al., 2019) (L. Zhang et al., 2021)
Metagenomics	Genetic analysis of samples containing different microbes	10^3 CFUml ⁻¹	- Detects microorganisms whether culturable or not Provides knowledge of microbial species present	- Inefficient expression of some metagenomic genes in the cloning vector and may not detect microbes present in very low concentrations	(Hinić et al., 2017)
Biochemical tests	The ability of bacterial to utilize specific substrates and produce certain end-products	10^4 CFUml ⁻¹ – >1600 cells/100 ml	- Inexpensive and easy to use The process does not require advanced laboratory set-ups	- Non-specific hence, unreliable Requires pre-enrichment hence, time-consuming	(Muhamad Rizal et al., 2020)
ELISA	Specific binding of antibodies to target antigens	1×10^3 CFUml ⁻¹ – 10^4 CFUml ⁻¹	- Very efficient and easy to perform Cost-effective due to affordable reagents	- Labour-intensive due to antibody preparations, and prone to false positive/negative results due to antibody instability	(L. Zhang et al., 2016; (X. Zhang et al., 2016) (Su et al., 2016) (Sakamoto et al., 2018)
IMS	Coupling of fragments of magnetic beads to target analytes through a specified antibody-antigen reaction	10^1 CFUml ⁻¹ – 10^2 CFUml ⁻¹	- Fast and easy to handle	- Prone to non-specific binding Sensitive to chemical agents	(Srisa-Art et al., 2018)(Lun et al., 2018)
NASBA	Amplification of multiple copies of RNA.	1 viable cell/100 ml – 7×10^{-1} CFUml ⁻¹	- Due to isothermal process, thermocycling equipment are not required. Relatively low detection limits and cost-effective	- Annealing of primer to targets is dependent on amplification reaction	(Zhai et al., 2019) (Heijnen and Medema, 2009)
LAMP	Automated cycling and displacement of DNA strands under isothermal conditions	6.7 CFUml ⁻¹ – 10 CFUml ⁻¹	- Cheap and utilizes low heating source	- Complex primer design and inability to carry out multiple amplification	- (Mei et al., 2019) (Lee et al., 2019)
PCR	Enzymatic amplification of nucleic acid	2.6×10^4 CFUg ⁻¹ – 3.5×10^3 CFUml ⁻¹	- Detects less commonly known organisms	- Relatively lower specificity than biosensors. High cost, training and installation cost	- (Paniel and Noguer, 2019)

sensitivity, LSPR has gained more acceptance than other techniques. LSPR occurs when surface plasmons are created due to the incidence of polarised light at the surface of a metallic conductor at the interface between two media such as liquid and glass, and a reduction in the intensity of reflected light at the resonance angle proportional to the mass on the surface (Damborský et al., 2016). With LSPR optical sensors, it is possible to reuse the sensor chips and closely monitor the binding of transducers to analytes in real-time (Roether et al., 2019) thus, allowing

the use of a wide variety of biosensing molecules such as nucleic acids and enzymes (Damborský et al., 2016).

More advanced optical biosensors incorporate biological receptors, material substrates, an amplified signal mechanism and a transduction approach. In particular, we would also like to highlight an optical sensor based on the LSPR principle for the detection of bacteria developed by our team (Funari et al., 2018). Here, large area pillared nanostructures, named gold nano-mushrooms were used to detect the biofilms of *E. coli*

as a proof of concept which can potentially be extended to other pathogens for the detection of biofilms in the environment and water samples. The extent to which the system was validated also consisted of antibiotic susceptibility tests in multiplexed formats. The results suggest that a combination of pathogenic biofilm detection and testing its resistance to drugs on the same platform can lead to advanced biosensing systems. For instance, on-site biofilms can be detected and a quick remedy for effective elimination of those biofilms can be provided by a rapid on-site drug susceptibility test. Fig. 4 shows the various optical sensing approaches.

(Vaisocherová-Lísalová et al., (2016) reported an SPR optical biosensor for the rapid and sensitive detection of bacterial pathogens in food. Using this method, they were able to detect *E. coli* O157:H7 at LOD of 57 CFU ml^{-1} and 17 CFU ml^{-1} in cucumber and hamburger respectively. They equally detected *Salmonella* species at LOD of $7.4 \times 10^3 \text{ CFU ml}^{-1}$ and $11.7 \times 10^3 \text{ CFU ml}^{-1}$ in cucumber and hamburger respectively. With the introduction of smartphone-based biosensors, biosensing has become cheaper and more user-friendly thereby offering more opportunities for use in various clinical settings and point-of-care testing while promoting self-testing (Yoo and Lee, 2016). Additionally, the smartphone-based biosensor can be used for real-time monitoring in a clinical setting such that the results could be transmitted automatically to a physician. Apart from the aforementioned nanoplasmonic sensor, the colourimetric, fluorescent and surface-enhanced Raman spectroscopy (SERS) based techniques can also be classified within the optical sensors, which have shown a great promise for pathogen detection, especially for the point-of-use application.

However, despite its suitability as a high throughput assay, the real-

life applications of optical biosensors in food safety, water quality and environmental monitoring have some limitations. First, the field is still evolving, and its application is currently limited within the academic arena and research institutes. Also, optical sensors may interact in a non-specific manner with targets in a complex sample matrix, resulting in the transduction of false signals. Optical sensors are equally affected by certain conditions such as pH, ionic strength and viscosity. Although some of these limitations may be overcome with commercial optical sensor kits, however, other challenges such as cost, instrumental designs and sensor calibration make the use of commercial kits an unsustainable solution for now (Ansari et al., 2017). Finally, large-scale experimental trials must be conducted to validate results gotten from biosensors (Yoo and Lee, 2016).

3.1.1. Lateral flow immunoassay

Lateral flow immunoassay (LFIA) is an immunosensor that visually detects the reaction between an antibody and its target substance in a sample. LFIA was developed through the integration of biosensors with immunological assay techniques to increase the sensitivity and specificity of such an assay. Generally, the technique involves the movement of the target substance present in a sample towards the antibody immobilised on the surface of a membrane strip. A change in the colour of the membrane strip indicates a result that shows the presence or absence of the target substance (Wang and Salazar, 2016; Välimaa, Tilsala-Timisjärvi and Virtanen, 2015). Based on their mechanism of action, immunosensors can be categorised as either label-based which involves the incorporation of a label to detect the antibody/antigen complex formation or label-free which involves the direct detection of

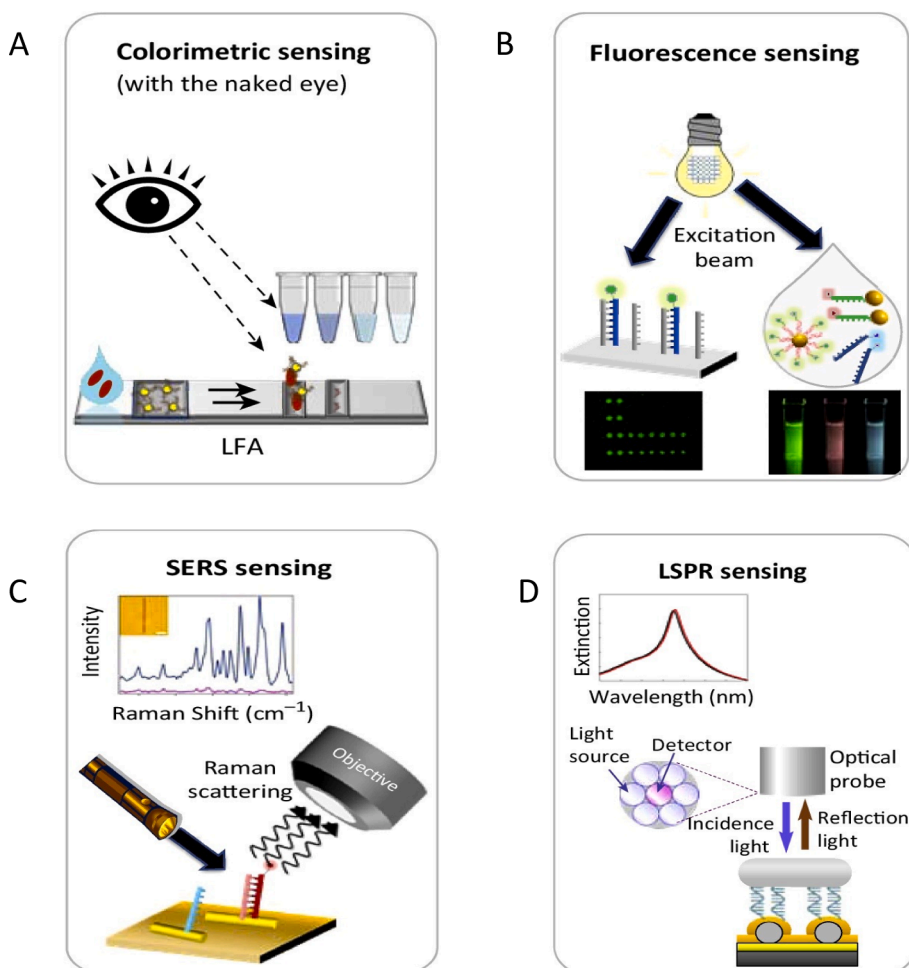


Fig. 4. Schematic illustrations of the various optical biosensors signal transduction sensing approaches used in an optical biosensor. (A). Colourimetric sensing approach; observation of visible colour change via the naked eyes. (B). Fluorescence sensing approach involving beams of electron. (C). Surface-enhanced Raman Scattering (SERS). (D) localised surface plasmon resonance (LSPR). LSPR provides a more rapid sensing advantage over other optical sensors. Reproduced with permission from (Yoo and Lee, 2016). Copyright 2016 Elsevier.

complex formed (Gheorghe et al., 2017; Patra et al., 2017).

The label-free method is preferable because it simplifies the entire assay process by reducing the number of reagents required and shortening the process involved thereby saving cost and time (Pirinçci et al., 2018; Duffy and Moore, 2017). The commonest types of LFIA are the antibody-based lateral flow assay (Sajid et al., 2015) and nucleic acid-based lateral flow assay (Chen and Yang, 2015). While the commonest labels used in LFIA include nanomaterials such as gold, silver and carbon nanoparticles, the gold nanoparticle is more widely used due to its high amplification effect (Jiang et al., 2015) although, other nanomaterials such as silver have higher signal amplification when combined with gold (Bhardwaj et al., 2019). Fig. 5 illustrates the principles of the label-free and label-based LFIA used to detect pathogens in food, water and the environment.

In a recent study, *E. coli* O157 and *Salmonella typhi* were detected from drinking water and milk samples using the LFIA technique with gold nanoparticles as label. In the study, the water and milk samples were prepared by spiking them with the bacterial pathogens to obtain a 10-fold dilution. Also, the colloidal gold nanoparticles were synthesised using the citrate reduction method. LFIA detected 7.8×10^5 CFUml⁻¹ and 3×10^6 CFUml⁻¹ of *E. coli* O157 in water and milk samples respectively. Also, LFIA detected 3×10^8 and 3×10^7 CFUml⁻¹ of *S. typhi* in water and milk samples respectively. The assay further showed 100% specificity for both bacteria, thus making this technique very vital for monitoring bacterial pathogens in food and drinking water (Mohammad et al., 2018). In another study, a novel immunosensor for the real-time detection of *E. coli* from food and water was proposed by (Srinivasan et al., 2017). The immunosensor was fabricated by immobilising anti *E. coli* antibody on the surface of the sensor which was then allowed to interact with strains of the bacteria in the sample. Specific binding between the anti *E. coli* antibodies and the *E. coli* pathogens generated a shift in the wavelength of the transducer which was detected using a fiber Bragg grating sensor (Srinivasan et al., 2017).

A major advantage of the LFIA is the speed and ease with which

samples can be analysed. The technique can be used to detect microbial indicator pathogens present in food, water and environment quickly and cheaper (Wang et al., 2016). Nevertheless, certain factors can affect the accuracy of the multiplexed LFIA such as sample flow. The technique has relatively low sensitivity, a higher rate of giving off false-positive results and requires enrichment (Wang and Salazar, 2016).

3.1.2. Aptamer-based immunosensors

Aptamers are DNA or RNA oligonucleotides that bind to a specific target molecule (pathogen) with high affinity and specificity very similar to the interaction between antigen and antibody (Li et al., 2019; Yeong et al., 2017). Aptamer-based immunosensors emerged as alternatives to antibody-based immunosensors due to the high cost of production of antibodies used in immunosensors. Generally, aptamers are between 25 and 90 bases in length and their usage in immunosensors provides some advantages over their antibody-based immunosensor counterparts. First, they have a high binding affinity, so they can bind to their complementary targets with high specificity. Secondly, aptamers have innate structural and temperature stability and can withstand the denaturation and reannealing process of nucleic acid amplification unlike antibodies therefore, they can be stored at temperatures above -20°C (Arshavsky-Graham et al., 2020). In addition, they can attach to small ligands such as nucleic acid thus, making them ideal in bacterial diagnostics especially when such ligands are the target molecules. Lastly, the synthesis of aptamers does not require animals or cell lines (Demirkol and Timur, 2016).

Aptamers are produced through a technological process known as the systematic evolution of ligands by exponential enrichment (SELEX) (Bayat et al., 2018), which allows the selection of bound live bacteria against other unbound non-targets such as proteins while non-targets are removed from the reaction through counter-selection (Hamula et al., 2016; Lorenz et al., 2010). It is vital to note that there is a direct relationship between the concentration of pathogens present in a sample and the signal displayed by a rapid sensor in use. However, this may not

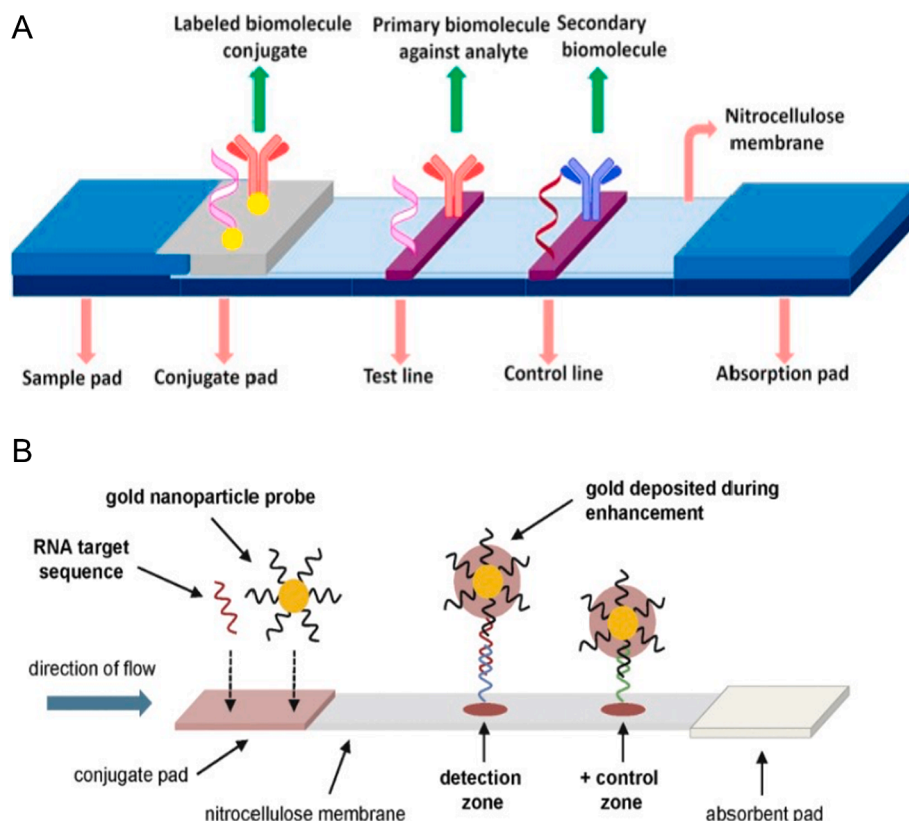


Fig. 5. Principles of a lateral flow assay. (A) Schematic of a lateral flow assay (Bahadır and Sezgentürk, 2016). A sample placed on the sample pad during assay moves gradually through capillary action towards the other end of the LFA strip. The sample pad is usually constructed using cellulose acetate or glass fiber due to their little or no affinity shown towards proteins. Reproduced with permission from (Bahadır and Sezgentürk, 2016). Copyright 2016 Elsevier. (B) A gold nanoparticle label-based immunoassay by (Rohrman et al., 2012).

always be correct especially when the biorecognition elements in a biosensor interacts with non-target analytes and displays a (false) negative or positive result. This is where the application of aptamer-based assays plays an equally vital role.

Through the SELEX technology, many aptamer-based assays can permit the selective binding of aptamers to their targets while excluding other non-targets. Interestingly, the LOD of many aptamer-based assays is close to the recommended guideline on safe food and drinking water thus, this makes them suitable for ensuring food safety and monitoring water quality (Majdinasab et al., 2018; McConnell et al., 2020). An important attribute of SELEX is that its production procedure which is chemical synthesis after the selection and sequencing of target genomes can be modified to increase their affinity and selectivity thereby making them suitable assay techniques for detecting microbial biofilms and other pathogens present in very low amounts even without enrichment (Meek et al., 2016).

However, the process is expensive and can equally result in an error due to multiple amplification also, some modifications could result in a structural change which may affect the selectivity and affinity of aptamers for the target pathogens thus, such modifications must be applied uniformly in the assay to ensure consistency (Fan et al., 2020; Mokhtarzadeh et al., 2016). Various researchers have fabricated aptamer-based assays for the detection of pathogens present in food and water (Amaya-González et al., 2013; Li et al., 2020; Yeong et al., 2017).

Bagheryan et al., (2016) designed a rapid label-free, portable plasmonic assay that can detect *Salmonella typhimurium* in pork meat samples under 30–35 min with a LOQ of 1×10^1 CFU ml⁻¹ and LOD of 6 CFU ml⁻¹ under optimal conditions. The setup featured a plasmonic sensor, with self-assembly of gold nanoparticles which gave off longitudinal wavelength extension shifts through an LSPR signal. The assay featured developed aptamers conjugated to LSPR sensing chips that can detect *S. typhimurium* in spiked pork meat samples without any pre-enrichment. Interestingly, the fabricated LSPR sensing chips were not prone to any form of contamination from the food matrix or other microflora, thus making this technique a very efficient means of detecting *S. typhimurium* in food samples.

Aptamer-based assay has also been developed for the detection of *E. coli* (Hua et al., 2018), *Vibrio parahaemolyticus* (Wu et al., 2018), *Pseudomonas aeruginosa* (Gao et al., 2018) and *Shigella dysenteriae* (Zarei et al., 2018) from food, water and environment with low LOD and high specificity in each case.

3.2. Electrochemical biosensors

Electrochemical biosensors convert the results of the interaction between a biorecognition agent and an analyte into electrical signals that are proportionate to the concentration of the analyte (Zhang et al., 2019). Based on the parameter being measured, electrochemical biosensors can be categorized as either amperometric which measures a change in current after binding of analytes and biorecognition agents, or impedimetric which measures impedance, or potentiometric which measures electric potential (Hameed et al., 2018). Xu, Wang and Li, (2016) constructed an electrochemical biosensor that can detect *E. coli* O157:H7 in food, water and environmental sample with a LOD of 10^2 CFU ml⁻¹. Despite being rapid, certain limitations exist in the use of electrochemical biosensors. For example, certain conditions such as the saturation energy of enzyme-substrate reactions and redox hindrances may affect the electrochemical process especially when the biorecognition agent is an enzyme (Wang and Salazar, 2016). Therefore, other biorecognition elements such as nanoparticles and nucleic acids could be used, for instance, non-functionalized gold nanoparticles have shown great promise in the detection of *E. coli* O157:H7 (Wan et al., 2016). Also, microbial pathogens are often not uniformly distributed in food, water, or environmental samples thus, the use of electrochemical techniques in detecting such pathogens becomes difficult, especially without sample preparations.

Another example of detecting pathogens using electrochemical sensors is with the use of field-effect devices. (Formisano et al., 2016) developed an extended gate field effect transistor functionalised with sugar-based biorecognition layers specific to the pathogenic *E. coli*. This particular sensor was developed with a modular approach consisting of a disposable electrode and a signal reader as shown in Fig. 6.

Additionally, the viscosity (liquid or solid) and physiochemical constituents of food could affect the biosensing process (Cesewski and Johnson, 2020). Thus, it is imperative to focus on developing novel biosensors with improved designs of analyte-biorecognition binding and amplified signal transduction to ensure effective results. To this effect, DNA-based nanosensors could be the way to go because unlike other biorecognition agents, they are very malleable and can accommodate any conformational change thus, making them able to detect binding activities during an analytical assay (Soukarié, Ecochard and Salomé, 2020; Xu, Wang and Li, 2017).

3.3. Mass-sensitive biosensors

Even though these sensors are not frequently used compared to the optical and electrochemical biosensors, the mass-sensitive biosensor technique involves the application of an alternating current of a given frequency to induce piezoelectric effects to measure the mass of the adlayer on the sensor surface (Yasmin et al., 2016). Any chemical reaction produced will affect the oscillation frequency, thus, these mass-sensitive biosensors measure changes in the frequency brought about by the interaction between a biorecognition element with an analyte. This technique is cost-effective, label-free and generally suitable for rapid detection of the analyte in portable formats (Guo et al., 2016b). In addition, mass-sensitive devices also use mechanical transduction methods based on either the generation or detection of acoustic waves/mechanical waves (Gaudin, 2017). The most common instruments used for mass-sensitive measurements include quartz crystal microbalance (QCM), piezoelectric crystals and surface acoustic waves (SAW).

However, the most popular amongst these instruments is the QCM because it is label-free and monitors the binding of analytes to biorecognition elements in real-time (Chen et al., 2018). Although various mass-sensitive biosensors have been fabricated for monitoring environment (Jain et al., 2019) (Justino et al., 2017) and the screening of microbial pathogens such as *Salmonella typhimurium* (Fulgione et al., 2018), *Campylobacter jejuni* (Masdor et al., 2016) and other pathogens (Eshrat and Subhas, 2017) in food, there are few reports on the development of QCM biosensors for water quality monitoring (Kumar et al., 2018; Nurliyana et al., 2018).

3.4. Microfluidic sensors

3.4.1. Traditional microfluidic sensors

Various attempts were made in the past to fabricate an integrated sample-to-answer analytical system in a single device and one of the successes of such attempts was the emergence of microfluidic sensors. Also known as Lab-on-a-chip (LOC). Microfluidic sensors refer to analytical sensors that can rapidly perform single or multiple laboratory operations on a portable chip. A distinguishing feature of LOC is that it allows the manipulation of very small quantities of fluid even smaller than the picolitre scale (Cole et al., 2017) and all the diagnostic protocols involved in standard laboratories from the sample preparation to the result stage are embedded in the device (Yang et al., 2017). Thus, making it relevant in LMIC. It is also relevant in LMIC in terms of cost, transportation and storage. Research has shown that a reduction in the area of analytical sensors could increase the sensitivity of the sensor while reducing the turnaround time of the assay (Lai et al., 2016) thus, the presence of microfluidic channels in a LOC device will increase the efficiency, accuracy and sensitivity of the device.

Three steps are involved in the point of care (POC) testing and they are the sample preparation, sample analysis and result interpretation.

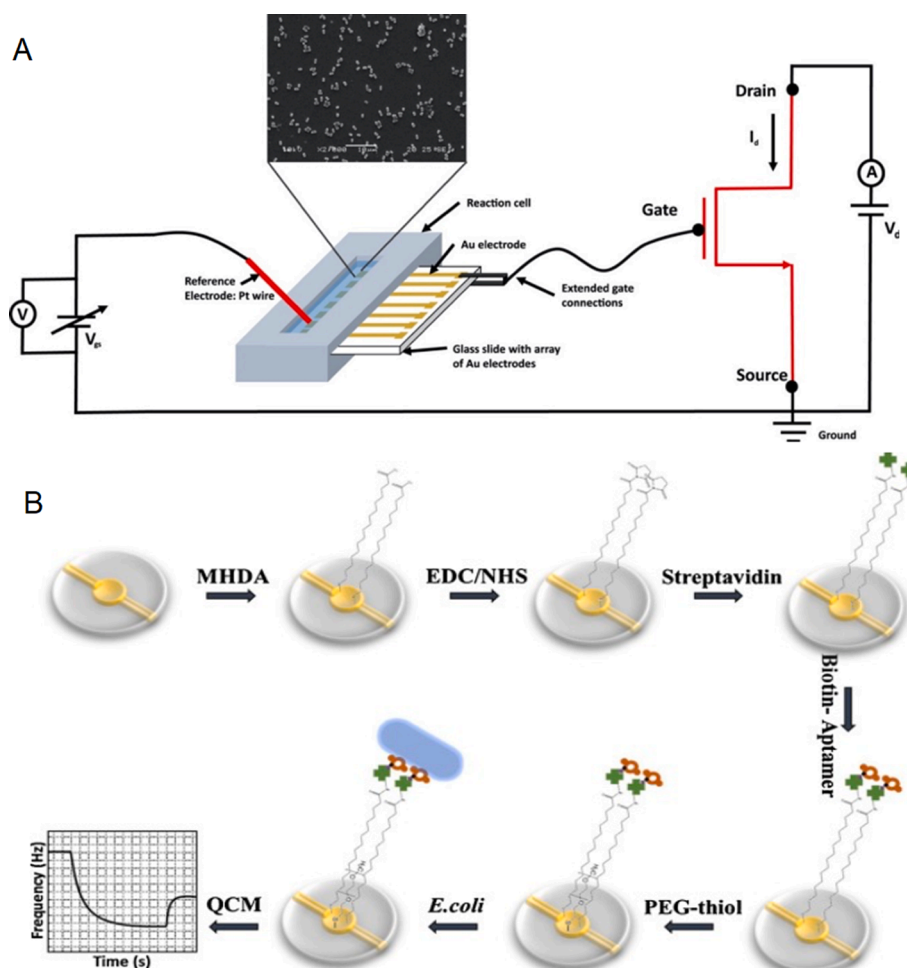


Fig. 6. (A) Working principle of the BioFET sensor. An array of evaporated gold electrodes placed in a flow cell is connected to the gate of a MOSFET. An external reference electrode is used to apply the gate voltage. Adopted from (Formisano et al., 2016) Biosensors and Bioelectronics. (B) Schematic diagram of the QCM aptasensor for the rapid detection of *E. coli* O157:H7. Adopted from (Yu et al., 2018).

Aside from its application in POC testing, the LOC has other several advantages which makes it a very powerful device. First, the low cost of fabrication encourages mass production. Secondly, the integration of small volumes and multiple functionalities make LOC systems very compact thus, allowing very high-throughput, automated and multiplexing assay (Samiei et al., 2016). Additionally, LOC offers other great opportunities such as biocompatibility, portability, real-time detection of pathogens with high accuracy (Wang et al., 2020). Furthermore, the design of LOC precisely controls the assay parameters such as channel size, the volume of sample, sample flow rate and reaction time. When compared to other techniques of detecting microbial pathogens, the LOC can process analytical samples at a very low cost with fewer materials (Gong and Sinton, 2017).

Finally, the short distances of LOC platforms promote rapid fluid movements and chemical diffusion thus, shortening the response time (Gupta et al., 2016). Generally, LOC offers a powerful and simple analytical tool and they have been designed to meet the diagnostic device standard for developing countries set by the World Health Organisation (WHO) which includes affordability, sensitivity, specificity, user-friendly, rapid and robust, equipment-free and deliverable to end-users (ASSURED) (Puiu and Bala, 2020).

Although LOC is affected by some limitations, researchers have come up with various ways to overcome such limitations. First, the transport of fluids in a microfluidic sensor channel is affected by evaporation and this is very critical because the limited sample volume lowers the size of the analyte which may affect the resulting readout. Also, analytical

samples may get contaminated by airborne particles or volatile organic compounds around the open fluid channels (Puiu and Bala, 2020). However, the development of LOC with faster wicking was able to combat this limitation (Fornells et al., 2018). Also, the development of enclosed fluid channels can reduce the evaporation of fluids and equally lower the risk of contamination due to exposure to an open environment (Strong et al., 2019).

The stability of the reagents and robustness of the microfluidic sensor devices is another limitation given that these devices are usually moved from the point of manufacture to where their application is more relevant such as resource-limited areas. The environmental conditions such as temperature and humidity of the two regions may differ and some LOC may not have any mechanism for regulating such environmental conditions (Shaw, 2016). However, with the evolution and ubiquity of smartphones, many LOC devices have been programmed to function with smartphones (Schönberger and Hoffstetter, 2016). This is possible because smartphones offer highly sensitive optical sensation with advanced processors thus, its incorporation lowers the complexities of sample analysis and results (Nasseri et al., 2018). Also, with the incorporation of smartphones to LOC, environmental conditions may have little or no influence over the assay procedure. Thus, eliminating the wrongful interpretation of results due to certain subjective conditions such as colour blindness (Morbioli et al., 2017). This ultimately makes LOC very relevant in LMIC.

3.4.2. Paper microfluidics

Microfluidic paper-based analytical devices (μ PADs) are LOC devices containing several hydrophilic cellulose fibres that precisely transport fluids from an inlet to a specified outlet through imbibition or capillary actions. This novel diagnostic system is a cheap but reliable means of analysing chemical and biological substances and therefore, is applicable in many low income countries where there is a limited number of healthcare professionals and diagnostic equipment (Budreviciute et al., 2020; Draper et al., 2018). Previously, microfluidic devices were fabricated using inorganic materials such as glass, silicon and ceramics however, other materials such as polymers (thermoplastics and elastomers) and paper were evaluated (Magro et al., 2017). So far, the paper has shown to be the most promising tool for fabricating microfluidic devices due to some reasons.

First, paper is readily available in many parts of the world at very cheap amounts. Paper allows movement of fluids through capillary actions thus, enables reagents to be immobilised on their surface. Also, the paper has high biocompatibility because it is primarily composed of cellulose (Carrell et al., 2019). Furthermore, the use of paper allows the flow of fluid along the surface without using a pump or electricity (Mao et al., 2020). Aside from these properties, other characteristics of paper that make it a convenient tool for incorporating into microfluidic devices include the ease of storage and transport of paper due to its low weight and thin size (Mao et al., 2020). The natural constituents of paper make it possible for organic compounds such as DNA and proteins to bind to the surface. Paper is highly inflammable thus any paper-based analytical assay can be burnt after usage (Reboud et al., 2019b). The background of white paper provides a sharp contrast against other coloured substances thereby making it an excellent material for microfluidic assay.

The integration of paper-based analytical devices with the LAMP technology has revolutionized the field of paper microfluidics (Cai et al., 2019; Anupama et al., 2019). The applications, merits and limitations of LAMP have been reviewed in the previous sections. The overall idea of the paper microfluidics was to use paper and replace the conventional microfluidic substrates such as silicon, plastics and polymers and a vital aspect in the design of paper microfluidic is patterning which is the design of the channels through which the fluids can flow through (Magro et al., 2017). The device also incorporates a fluid control valve which alters the rate of the fluid flow by joining or separating cut channels along the paper. Microfluidic fluid patterning can be done using techniques such as cutting (Leu et al., 2018), photolithography (Brower et al., 2017), etching (Bandara et al., 2018), wax-printing (Ma et al., 2018) and three-dimensional (3D) microfluidic paper-based technology (Fang Li et al., 2019).

The most popular of these techniques is the wax printing technique that can easily create a hydrophobic barrier-channel that can control the direction of the fluid flow in about 5 min (Magro et al., 2017). Four methods of paper-based microfluidics are available for the detection of analytes and they include Electrochemical detection, Colorimetric detection, Chemiluminescence, and electrochemiluminescence detection methods (Akyazi et al., 2018). The most used method of detection is colourimetry with an enzymatic colour change that can be visible to unaided eyes. The colourimetric technique is also very popular because it offers instrument-free quantification and easy readout (yes or no) (Yang et al., 2017).

To buttress its popularity, Kim et al (Kim and Yeo, 2016) developed a rapid paper-based analytical device using wax printing for *in situ* colourimetric detection of *E. coli* in environmental water samples. The technique is a modification of the catalase test with Fenton's reaction which also includes a colour indicator that changes according to the concentration of *E. coli* bacteria present in a sample. For a single-color detection test, 20 μ L of hydrogen peroxide solution was used, and the detection chambers were loaded twice with 1 μ L of ferrous sulfate and subsequently dried. This method proved to be significant in the detection of *E. coli* in environmental water samples (Kim and Yeo, 2016).

Sweet et al presented two new colourimetric microfluidic techniques for on-site detection of infectious pathogens in drinking water. the first system is a proposed handheld manually actuated microfluidic device while the second is a customised drop-casting protocol used to pre-load a 3D printed device that was fabricated through an ultra-high-resolution additive manufacturing technology for the detection of *E. coli* in drinking water samples with a LOD of 10^6 CFU ml^{-1} in 6 h. The proposed microfluidic system will enable on-the-site water quality testing while encouraging higher analytical throughput (Sweet et al., 2019).

Although many advances have been made to simplify paper-based microfluidics and one of such is the integration of smartphones into paper-based microfluidics as shown in Fig. 7.

4. Conclusion and perspectives

Biosensors for monitoring bacteria contaminants in food, water and the environment can be considered as a robust and more accurate technique compared to the traditional techniques. Evidence has shown that rapid analytical sensors are not only used in medical diagnosis but also in the analysis of food and various water and environmental samples. Currently available analytical sensors are suitable for monitoring pathogens in food and the environment however, they may not be very suitable for use in the assessment of drinking water quality due to their sensitivities which do not fall within the range of values recommended for drinking water quality. However, this can be further improved within different technology including transdisciplinary technology to significantly improve the performance.

Although the miniaturization of sensors such as microfluidic sensors is desirable for simplicity, storage and transportation, however, there is a limitation on the total volume of aliquots that could be analyzed from various samples such as water. Therefore, such analysis may not be a true representation of the quality of the water source tested. For instance, if the test result for *E. coli* or other total coliform bacteria in any water sample is negative, it is not a guarantee that bacteria contaminants are absent in the water, especially considering that these pathogens may not be uniformly distributed in the water sample and the chances of testing the portion containing the pathogen are uncertain. Thus, numerous tests must be conducted randomly to validate any results gotten before making any informed public health decisions. Hence, further research needs to be conducted to fabricate a multiplexed high-throughput device for efficient and high performance on-the-site assay that can limit the chances of false hits while ensuring early detection of bacterial contaminants in food, water and the environment.

The sensitivity of these rapid sensors also varies according to the sample matrix analyzed therefore, the combination of advanced sample processing techniques is vital to validate obtained assay result before making any public health decision, because one technique may not be sufficient to confirm the presence of a pathogen considering the low chance of pathogens being present in an aliquot. These biosensors have shown to be promising in the detection of bacterial pathogens present in contaminated drinking water. However, more optimization works is still required to overcome the problems of non-specific binding of bio-recognition agents to non-target analytes. Nevertheless, because biosensors offer promising portability and very significant detection limits, public health experts in low resource setting should make informed decisions based on local context after considering the benefits and flaws of each option selected. Additionally, further study is required to develop a novel rapid sensor that can accurately detect bacterial pathogens present in a sample despite the volume of aliquots. Thus, future research should focus on the design and fabrication of a multiplexed analytical sensor that can integrate more than one assay technique in a device to ensure the optimal sensitivity and best performance of such assay while considering the costs. This will lead to faster turnaround time and efficient diagnosis.

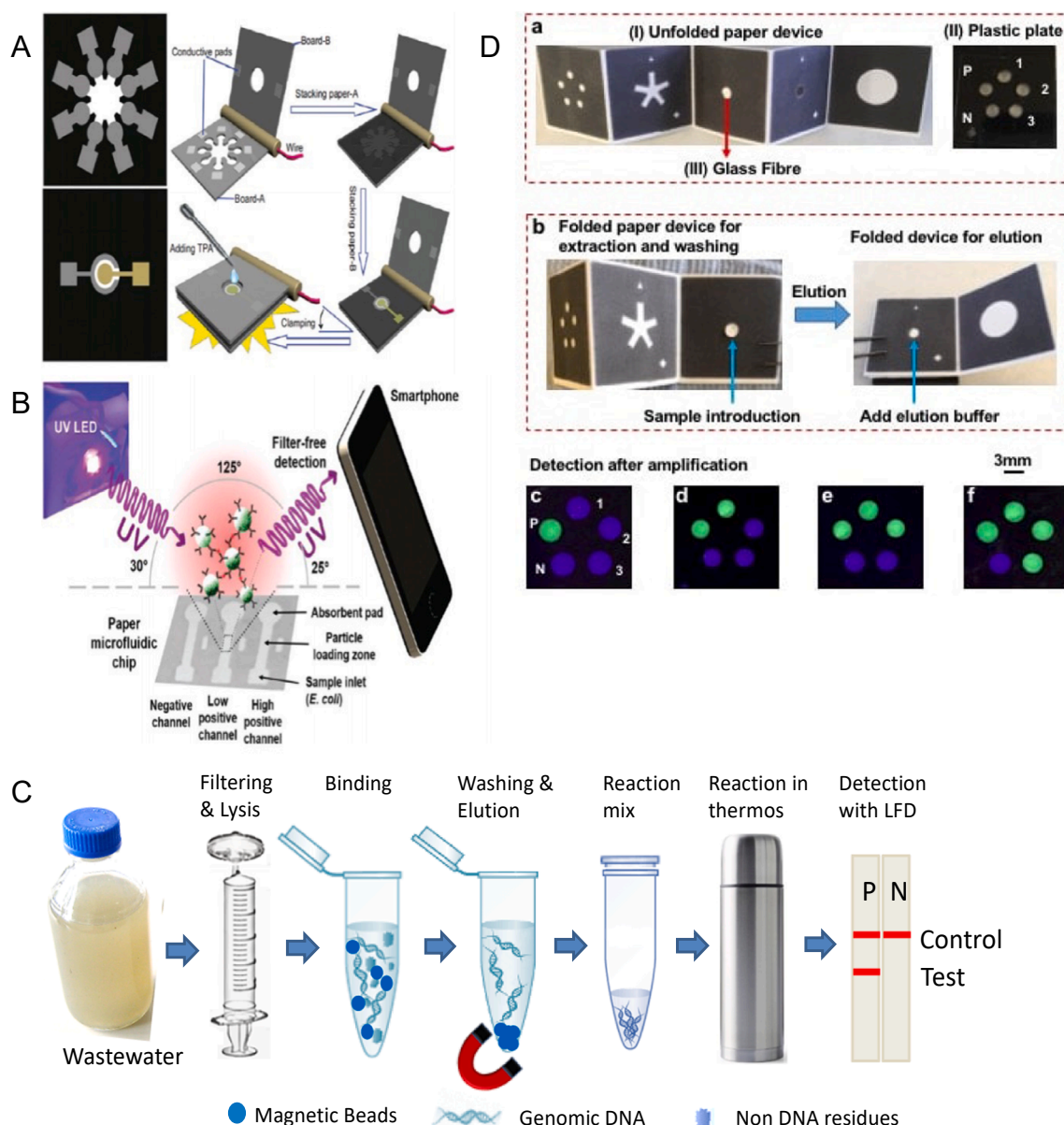


Fig. 7. Detection techniques using μ PADs. (A) the fabrication process of a portable paper-based microfluidic sensor for multiplexed detection of target analytes. Reproduced with permission (Ge et al., 2012). copyright 2011 Elsevier Ltd. (B) integration of a portable smartphone with paper-based microfluidic sensors for easy result readout. Reproduced with permission (Park et al., 2017). Copyright 2016 Society for Laboratory Automation and Screening. (C) Schematics of a LAMP of nucleic acid biomarkers from raw untreated wastewater samples, Yang et al., 2017 Anal. Chem., 2017, 89: 99415. (D) Multiplexed paper device for detection of 3 targets (1, 2, and 3) with internal positive (P) and negative control (N) for visual detection of pathogens,

CRedit authorship contribution statement

Raphael Chukwuka Nnachi: Conceptualization, Writing – original draft, Visualization. **Ning Sui:** Writing – review & editing. **Bowen Ke:** Writing – review & editing. **Zhenhua Luo:** Writing – review & editing. **Nikhil Bhalla:** Writing – review & editing. **Daping He:** Writing – review & editing. **Zhugen Yang:** Conceptualization, Writing – original draft, Visualization, Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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