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BioFET-based Integrated Platform for Accurate and Rapid Detection of *E. coli* Bacteria: A Review

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Abstract

Enteric and diarrheal diseases are major causes of childhood illness and death in countries with developing economies. Each year, more than half a million kids under the age of five die from these diseases. *Escherichia* coli, *E. coli*, a water/foodborne pathogen, is one of the major sources of food poisoning which results in severe diarrhea at extremely low concentrations and therefore is very challenging to be detected. Using available technologies, which are mostly based on amplification of low concentration samples, to detect the presence of the bacterium takes several hours to days; thus, a fast and an accurate detection alternative is on demand over lab-based technologies. In this sense, emerging nanoscale bio-transistors enable quantitative detection mechanism based on electrochemical binding of circulating analytes to immobilize antibodies on the biodevice's active surface. The state of the art of the Bio Field Effect Transistors (BioFETs) for fast track and accurate detection of *E. coli* is the concern of this review paper which describes and compares the recent advancements in the field. Furthermore, implications for novel approaches to different configurations based on the sensing principles and corresponding parameters are elaborated and discussed in detail.

Keywords: *E. coli* Bacteria Cells; Biosensors; BioFET; BioCMOS

Introduction

E. coli, a gram-negative rod-shaped bacterium with more than 150 serotypes discovered in the human colon in 1885 by German bacteriologist Theodor Escherich, is considered an important group of bacterial enteropathogenesis. Many serotypes of the bacterium are usually harmless and live in the gut of healthy people and can benefit their hosts by producing vitamin K2, and by preventing the establishment of pathogenic bacteria within the intestine. However, some, such as O157:H7, O104:H4, O121, O26, O103, O111, O145, VTEC O157, and O104:H21 cause common infections such as urine infections and gut infections (gastroenteritis). The VTEC O157 is a less common cause of infection but can lead to a severe gut infection with bloody diarrhea and other serious diseases such as Haemolytic-Uraemic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP). O104:H4 is a virulent strain that was behind the deadly *E. coli* outbreak in Europe in June 2011. O157:H7, discovered in 1982, is also notorious for causing serious and even life-threatening complications such as HUS. During an outbreak in the western United States in late 1992 to mid-1993, many people became infected with the virus after the consumption of hamburger; some were hospitalized and a few died. Between 2003 and 2012, the Centers for Disease Control and Prevention (CDC) traced 391 O157:H7 outbreaks, including 4,930 cases of the illness, with 1,274 hospitalizations (26%), 300 cases of HUS (6%), and 34 deaths. Based on CDC reports, the beef (55 percent of the outbreak) was diagnosed as the most common food source for this bacterium. Leafy greens and dairy and all other types of meats and poultry were also found to represent 21, 11 and 6 percent of the food sources, respectively [1].

E. coli consists of various groups of bacteria. Pathogenic *E. coli* strains are categorized into pathotypes. Five pathotypes, as explained below, are associated with diarrhea and collectively are referred to as diarrheagenic *E. coli* [1-3].

Shiga toxin-producing E. coli (STEC) may also be referred to as Verocytotoxin-producing *E. coli* (VTEC) or enterohemorrhagic *E. coli* (EHEC). This pathotype is the most commonly heard about in the news in association with foodborne outbreaks. EHEC strains are characterized by the production of influential cytotoxins called Shiga toxins (Stx1 and Stx2) or verotoxins that induce microvascular changes in vivo and are the major virulence factor linked to paralytic and lethal cases in mice, and are cytotoxic for selected cell lines *in vitro*.

- *Enteropathogenic E. coli (EPEC),* unlike VTEC, do not produce any classic toxins. Their virulence mechanism involves the formation of A/E lesions followed by interference with host cell signal transduction. Following the ingestion of EPEC, the organisms adhere to the epithelial cells of the intestine, causing either watery or bloody diarrhea.
- *Enteroaggregative E. coli (EAEC)* are associated with acute or persistent diarrhea, especially in developing countries. Infection is typically followed by a watery, mucoid, diarrhoeal illness with little to no fever and an absence of vomiting. The precise mechanisms by which EAEC cause diarrhea and the role of the various pathogenicity factors are poorly understood. EAEC strains are characterized by their ability to adhere to tissue culture cells in a distinctive "stacked, brick-like" manner.
- *Enteroinvasive E. coli (EIEC)* is transmitted through the fecal-oral route. Even minimal contact is adequate for transmission. Following the ingestion of EIEC, the organisms invade the epithelial cells of the intestine resulting in a mild form of

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dysentery often mistaken for dysentery caused by Shigella species.

Enterotoxigenic *E. coli (ETEC)* is a major cause of traveler's diarrhea worldwide. Infection with ETEC leads to watery diarrhea which lasts up to a week but can be protracted. Upon infection, ETEC first establishes itself by adhering to the epithelium of the small intestine via one or more colonization factor antigens (CFA). This is followed by the expression of one or more heat-stable (ST) or heat labile (LT) enterotoxins.

At the moment, the traditional diagnoses of pathogenic *E. coli* O157:H7 mainly rely on conventional cell culture, microscopic analysis, and biochemical assays, which are laborious and time-consuming procedures and require special equipment and trained users. Over next sections, we will briefly report some of the methods used to detect the bacterium.

As has been mentioned above, the most frequently used techniques to detect *E. coli* are based on conventional methods including culturing and colony counting, polymerase chain reaction (PCR), and enzyme-linked immunosorbent assay (ELISA) because of their sensitivity to target microorganisms, efficiency, reproducibility, and suitability to a wide range of food matrices, and they are considered to be more reliable options to confirm results obtained on the presence of the pathogens [4,5]. Persson et al. and Tong et al. [6,7] developed an indirect ELISA for the efficient detection of *E. coli* infection in cattle. They utilized a simple, rapid and convenient method for detecting the infection of *E. coli* with different serotype strains. In this procedure, with the relative sensitivity of 100% and specificity of 96.47%, the recombinant OmpT (an aspartyl protease) has been applied as a capture antigen in the ELISA.

A direct PCR (DPCR) has also been developed for the detection of the STEC including tracing O157:H7 in environmental as well as other samples [8]. The detection procedure takes place by applying specific primers to water and milk samples to encode Shiga toxin genes and is performed using whole cells without DNA extraction. This simple method could potentially be an alternative for existing techniques or may be used in conjunction with other conventional methods; with the aim of reducing the complexity and time for the assay, a direct detection of amplified toxins, taken directly from *E. coli* cultures, can be made.

In another experiment and to compare the results, two culture-based and three PCR-based methods have been employed for detecting of *E. coli* O157:H7 in minced beef [9]. Minced beef samples have individually been tested with five distinct strains of *E. coli* O157:H7 (17 and 1.7 CFU/65g) and then exposed to the various testing methodologies. The PCR-based methods were the same to detect the *E. coli* O157:H7 in the minced beef at 1.7 CFU/65g. Although the culture-based system detected more positive samples compared to the PCR-based one, its detection time was longer than the PCR-based method.

In low- and middle-income countries, a simple, low-cost diagnostic device to detect *E. coli* in water and at a clinic would have a significant impact. In light of this situation, a simple paper-based colorimetric platform was developed to detect *E. coli* contamination in 5 h [10]. The technique is less time-consuming, easier to perform, and less expensive than conventional methods, making it an innovative point-of-care diagnostic (PoCD) tool to rapidly detect *E. coli*. It could potentially be applied to other pathogens, especially in places where there is a lack of advanced clinical equipment.

Despite the advantages, all of the conventional methods require amplification of the bacterium in a sample and tend to be laborious, time-consuming, expensive, require highly trained personnel, and cannot be used on-site, resulting in a delay in response during the spread of epidemic outbreaks. Hence, it is extremely important to develop new techniques for the detection of *E. coli* with label-free, rapid, portable biosensors to prevent catastrophic explosions of diseases caused by the public consumption of contaminated foods and drinks.

The aim of this work is to report both the early stages and the state-of-the-art of detection methods for pathogenic bacteria, with focus on advanced detection techniques, in particular, the integrated on silicon ones. To this end, the remaining parts of this manuscript include a description of main biosensing techniques in Section II. In Section III, biosensors intended for bacteria detection are summarized. Section IV deals with submicron transistors-based sensing devices is discussed. Finally, conclusions about discussed methods and devices are the subject of Section V.

Types of Biosensors

The term of "biosensor" refers to an analytical device composed of a biological receptor and a physical or chemical transducer that can specifically recognize and capture the target analyte and convert the biological and/or chemical phenomenon into quantifiable and analyzable signals, as shown in Figure 1. As demonstrated, the biological receptors used in a biosensor could be an antibody, an aptamer, an enzyme, a ssDNA/RNA probe, a bacteriophage, and so forth [10-16].

Based on the transduction mechanism, biosensors are classified into four major types [17-23] 1) Optical-including light absorption/reflection, surface plasmon resonance (SPR), fluorescence, luminescence, and optical fiber; 2) Piezoelectric-including quartz crystal microbalance (QCM), surface acoustic wave, magnetoelastic, and cantilever; 3) Electrochemical-including amperometric/voltammetric, potentiometric, impedimetric, and conductometric; and 4) Colorimetric—including conventional thermistors, enzyme thermistors, thermopile sensors, etc., working based on the detection of heat produced from biological reactions caused by enthalpy changes [24]. These main types of biosensors will be thoroughly described in the next Section with a focus on the detection of *E. coli*.

After briefly introducing the properties of biosensors, it is important to have a look at the reported statistics in this field. A survey of papers published from 2000 to 2015 [1] demonstrates that optical and electrochemical biosensors are the most frequently reported studies on the detection of *E. coli* O157:H7, as can be observed in Figure 2. However, optical biosensors encounter some constraints such as manufacturing expenses and short-term stability of the immobilized reagents under an incident light, while the electrochemical biosensors

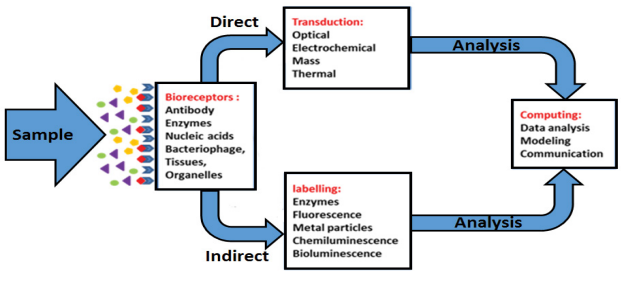

Figure 1: Main components of a typical biosensor.

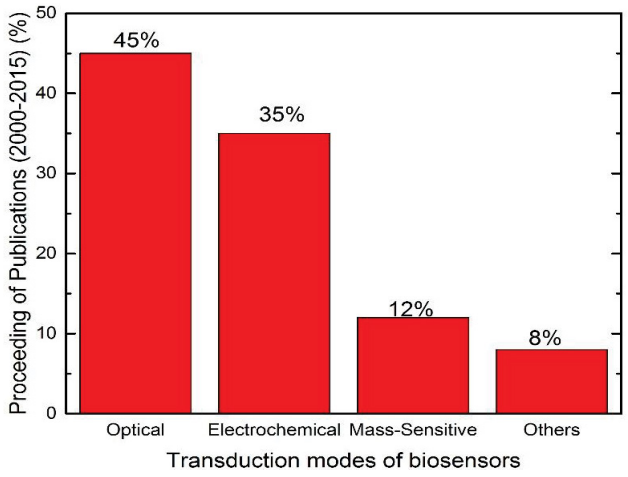

Figure 2: Approximate number of publications that use biosensor methods for the detection of *E. coli* O157:H7 [2].

suffer from drawbacks related to bacterium detection difficulties because of an extremely improbable distribution of the bacterium in the samples. Furthermore, the selectivity and the low limit of detection (LoD) of the electrochemical biosensors are also a concern, especially to the bacteria, with no health risks that can show a false positive result and for the detection of small quantities of *E. coli* O157:H7 in the samples [2,25,26].

For the purposes of commercialization, three main issues must be considered in the design of a biosensor:

a) the stability and preservation of the biological materials,

b) the consistency of the biosensors under different working conditions, and

c) the accuracy when dealing with the complex matrices of the real foods [2,27].

In this case, researchers have recently focused on the development of features including bioreceptors and novel nanoparticles for an effective reaction. Furthermore, it has been found that environmental conditions such as temperature, pH, and humidity impact the bioactivity of the biomaterials in biosensors [26,27]. The sensitivity of a biosensor becomes less efficient over time, which will greatly affect the performance of assessments, in particular in the case of electrochemical assays. Currently, most studies have focused on the development of new conductive nanoparticle materials and nucleic acid-based bio-recognition elements to replace the traditional antibodies (Abs) or enzymes. These molecules and chemicals have the advantages of being low-cost, stable, and comparable efficiency with their counterparts to improve sensitivity and stability. Table 1 summarizes the desired performance and the main features of a biosensor intended for the detection of pathogens.

Methods for Detecting *E. coli*

In the previous section, the various types of biosensors that are categorized based on transducers are introduced and compared on the whole. Here, to make a more precise comparison, the recent methods presented surrounding the detection of *E. coli O157:H7* is considered individually. Characteristic parameters of every procedure have been extracted and summarized, as elaborated in the following sections.

Optical biosensors

Optical biosensors have been applied mainly to healthcare, environmental applications, and the biotechnology industry [28-31]. These biosensors suggest some advantages over conventional analytical techniques as a result of the direct, real-time and label-free detection of many biological and chemical substances.

The surface plasmon resonance (SPR) with a very high sensitivity is the most common method, other than optical ones, to detect the foodborne pathogenic. In SPR, which employs reflectance spectroscopy for the detection of a pathogen, the electromagnetic radiation of a certain wavelength interacts with the electron cloud of a thin metal layer and produces a strong resonance. When the pathogen binds to bio-receptors immobilized on the surface of a metal layer, this interaction alters its refractive index, which results in the change of wavelength required for electron resonance. Table 2 demonstrates some optical methods surrounding the detection of *E. coli*.

Electrochemical biosensors

Electrochemical biosensors are considered to be low-cost, miniaturized, easy-to-use and portable devices for a wide range of applications, in particular medical diagnosis and environmental monitoring. This type of sensor operates by reacting with the analyte to produce an electrical signal proportional to the concentration of target molecules in the analyte. A typical electrochemical sensor consists of a sensing electrode (working electrode) and a reference electrode separated by an electrolyte. For most applications, a three-electrode system is used with the reference connected to a high-input-impedance potentiostat and a counter electrode is used to complete the circuit for current flow. An electrochemical biosensor is generally classified into several different types such as amperometric, impedimetric, potentiometric, and conductometric according to the measurement of changes in current, impedance, voltage, and conductance, respectively, which is caused by antigen-bioreceptor interactions. Many researchers have reported the successful detection of foodborne pathogens by electrochemical biosensors; Table 3 shows main works intended to the detection of *E. coli* [30-38].

Mass-based biosensors

Mass-sensitive biosensors operate based on the sensing of small changes in mass [39,40]. These biosensors are composed of piezoelectric crystal, which will vibrate at a certain frequency, induced by a sensible change of mass. Binding the target molecules to the receptors immobilized on the crystal creates a measurable change in the vibrational frequency of the crystal, correlated with the added mass on the crystal surface. The mass-based biosensors are categorized into two major types; the bulk acoustic wave resonators (BAW) or quartz crystal microbalance (QCM) and surface acoustic wave resonators (SAW). Although these types of sensors are used in various detection fields, nonetheless in terms of foodborne pathogen detection, their application is generally less than electrochemical and optical biosensors [41-43]. Some devices relevant to *E. coli* detection have been summarized in Table 4.

From a comparison of the aforementioned methods, a summary of their advantages and drawbacks is provided in Table 5. In order to deal with the drawbacks mentioned earlier, researchers have been inclined to develop high-performance devices conducting appropriate structures and synthesis alternative receptors; aptasensor, with its unified features, is one of the devices that refine some properties of biosensors, such as stability and selectivity [44,45].

Properties	Value or quality
Sensitivity	Less than 10 cfu/mL
Specificity	Can identify a specific target strain from other serotypes in the same or different species (e.g., can distinguish *E. coli* O157:H7 from other *E. coli* or Salmonella Minimum background noise (minimum unspecific binding from the food matrices)
Detection time	Real-time
Size	Portable, compact instrumentation can fit into a suitcase
Consistency	The test can be performed under different conditions at the site of interest, and test results have no significant difference to those done at laboratory
Stability	The biorecognition elements or biochemical labels should be stable for months under normal conditions for simple preservation
Sample processing	Minimal pre-treatment of sample, simple test procedures (better to be label-free)
Operator requirements	No special training needed to use the assay, can be used by individuals at home

Table 1: Properties of an ideal biosensor for the detection of foodborne pathogens.

Mode of transducers	Bio-recognition	Detection				Ref
	Immobilization of Ab & Functionalization	Label	Detection time	Detection range Culture	Food	
Photonic	✓ To immobilize a network of biotinylated antibodies interfaced with biotinylated polyethylene glycol thiols through the link provided by neutravidin. ✓ Post-processing of thiolated samples in ammonium sulfide was applied to increase the stability of the biosensing architectures while allowing biosensing at an attractive level of detection	NA	64.5 ± 1.1%, 77.0 ± 1.8%, 90.5 ± 3.9%	10^3,10^4,10^5 (cell/ml)	PBS	[32]
Surface Plasmon Resonance	✓ The surface is subsequently functionalized by the formation of a mixed self-assembled monolayer (SAM) by incubating the cleaned substrate in ethanol with 0.7 mM 11-mercapto-1-undecanol (C11OH) and 0.3 mM 16-mercaptohexadecanoic acid (C15COOH) at room temperature ✓ Monoclonal antibody immobilized onto a mixed –COOH and –OH-terminated SAM of alkanethiols on a gold surface	Label free	10 to 60 min	Samples 10^3-heat-killed samples 10^5-untreated samples 10^6	PBS with 1 mg/ml BSA	[33]
	✓ The activation process performed by NHS-EDC ✓ Lectins were immobilized onto the surface of CM5 chip through an amide bond	Label free	Real-time	3×10^3		[34]
	✓ After activation with EDC/NHS, anti-*E. coli* O157: H7 antibody was immobilized on the gold surface ✓ Then the ethanolamine was injected	Label free	5 to 7 min	3×10^5		[35]

Table 2: Optical biosensors presented for the detection of *E. coli*.

Mode of transducers	Bio-recognition	Detection	Detection			Ref
	Immobilization of Abs & Functionalization	Label	Time	Range Culture	Food	
DNA Electro-chemical	✓ Magnetic cobalt particles modified with alginic acid were used for isolation of microbial DNA of *E. coli*. ✓ The NH2 labeled oligonucleotide DNA probe was immobilized to magnetic beads for magnetic separation of the conjugated samples. ✓ Daunomycin (DNR) was used as DNA hybridization indicator	NH_2 Labeled	>10 min for *E. coli* DNA hybridization detection	10^2 to 2×10^3 (cell/ml) and 10 (cell/ml)	PBS and water	[36]
Ampero-metric	✓ (AEAPS) interlayer and an Au nanoparticles shell (denoted as Au-AEAPS-PB-Fe_3O_4). ✓ The immunomagnetic anti-*E. coli* O157: H7/Au-AEAPS-PB-Fe_3O_4 beads were prepared through the Au-SH bond between the antibodies of *E. coli* O157:H7 anti-*E. coli* O157:H7) and Au-AEAPS-PB-Fe_3O_4. ✓ Blocking with BSA	Labeled	NA	detection limit of 4.3×10^2 from 3.6×10^3 to 3.6×10^6 (cfu/ml)	PBS	[37]
	✓ SPE/MWCNT-PAH/ABs	Respective Abs Conjugate with CdS, CuS, or PBS Nano-crystals	>1 h	800, 400, and 400	Milk	[38]
	✓ Bare SPCE	MBs-1st AB +AuNPs-2nd AB	>1 h	148 in buffer, 457 in minced beef, and 309 in tap water		[39]
Impedi-metric	✓ Graphene paper was prepared by chemical reduction of Graphene oxide paper obtained from vacuum filtration method ✓ The gold nanoparticles were grown on the surface of Graphene paper Electrode by one-step electrodeposition technique ✓ The immobilization of anti-*E. coli* O157: H7 antibodies on paper electrode were performed via biotin-streptavidin system	Label free	NA	1.5×10^2 to 1.5×10^7 (cfu/ml)	Ground beef & cucumber	[40]

Table 3: Electrochemical biosensors presented for the detection of *E. coli*.

Mode of transducers	Bio-recognition		Detection			Ref
	Immobilization of Ab & Functionalization	Label	Time	Range culture	Food	
Mass-piezo	✓ The polyclonal antibody, anti *E. coli* rabbit IgG was used as the biomolecular recognition element ✓ The antibody is immobilized onto the surface of MSMC with freshly gold-coated surface using physical absorption.	-	Real-time (less than 5min)	10^5 to 10^9	Water	[43]
	✓ The chip is functionalized with poly-l-Lysine ✓ Three integrated electrodes. The first electrode is the doped silicon, the second electrode is the gold strip at the fixed end, the third electrode is the gold strip	Label-free	Real time	10^5, 10^6, 10^7 (cell/ml)	Water	[44]
	✓ A thiolated single-stranded DNA (ssDNA) probe specific to *E. coli* O157:H7 eaeAgene was immobilized onto the QCM sensor surface through self-assembly. ✓ The hybridization was induced by exposing the ssDNA probe to the complementary target DNA-streptavidin conjugated Fe_3O_4 nanoparticles	Biotin-labeled primers	Less than 1 min	2.67×10^2 to 2.67×10^6	PCR products	[45]
	✓ Au nanoparticles were immobilized onto the thioled surface of the Au electrode. ✓ Thiolated single-stranded DNA (ssDNA) probes could be fixed through Au-SH bonding. ✓ The hybridization was induced by exposing the ssDNA probe to the complementary target DNA of *E. coli* O157:H7 gene eaeA	Label free	Real time	2×10^3 (cfu/ml)	products	[46]

Table 4: Mass-based biosensors presented for the detection of *E. coli*.

Detection method		Advantages	Limitations
Biosensor-based	Optical	• High sensitivity • Enables real-time or near real-time detection • Label-free detection system	• High cost
	EElectrochemical	• Can handle large amounts of samples • Automated • Label-free detection	• Low specificity • Not suitable for analyzing samples with few microorganisms • Analysis may Interfere with Food matrices • Many washing steps
	Mass based	• Cost-effective • Easy to operate • Label-free detection • Real-time detection	• Low specificity • Low sensitivity • Long incubation time of bacteria • Many washing and drying steps • Regeneration of crystal surface may be problematic

Table 5: Advantages and limitations of above described detection methods.

Aptasensors

The discovery of Systematic Evolution of Ligands by an Exponential Enrichment (SELEX) assay has led to the generation of aptamers from libraries of nucleic acids [46-53]. These single-stranded DNA, RNA, or modified nucleic acids possess unique properties that make them superior biological receptors to antibodies with a plethora of target molecules. Some specific areas of opportunities explored for aptamer-target interactions include biochemical analysis, cell signaling and targeting, biomolecular purification processes, pathogen detection and clinical diagnosis and therapy [54,55]. Most of these potential applications rely on the effective immobilization of aptamers on support systems to probe the target species.

Aptamers, since they have an exclusive secondary structural conformation, are able to distinguish between various targets or enantiomers based on the conformational differences in the structures of target molecules. Additionally, aptamers can be an efficient alternative to conventional receptors such as antibodies based on some advantages, including:

- Much smaller size
- Have non-covalent bonding or fold around small molecules
- More easily modified at terminal sites with several functional groups
- More stable than antibodies against both reducing conditions and heat denaturation
- Typical aptamers are shorter than 40 nucleotides (nts) and easy for high-quality production by chemical synthesis

At this point, it is noteworthy that some researchers have attempted to amend the procedure for the detection of *E. coli* with the aptamer. The impact of an aptamer as a bioreceptor has apparently emerged in the detection time and range. In addition to the consequences summarized in Table 6, Marton et al. used cell-SELEX to isolate four single-stranded DNA (ssDNA) aptamers that bind strongly to *E. coli* cells (ATCC generic strain 25922) [56]. Specificity tests with twelve different bacterial species showed that one of the aptamers is highly specific for *E. coli*.

The methods described in previous sections are mostly multi-stage processes, time-consuming and expensive. Therefore, there is significant demand to develop manufacturing processes that can reliably and reproducibly generate functional nanostructures at low cost and in large quantities for implementation in practical integrated devices. The development of field portable monitoring devices, such as the field effect transistors (FETs)-based biosensors, has increased during the past decade. These devices show attractive prospects, which will be broadly applied in clinical diagnosis, food analysis, process control, and environmental monitoring in the near future [57,58].

Bio-FET

Biotechnology needs very cost-effective, intelligent biochips for analysis and multi-component detection for portable devices that use smaller sample volumes and have faster read-outs [59]. In this regard, biosensors, based on FETs, generally called (Bio-FET), drew attention to the fact that they could easily be integrated into a low-cost array of sensors for the simultaneous screening of large panels of analytes [60-64]. Additionally, these devices have shown great promise as a

Bio-recognition (Mode of transducers)		Detection			Ref
Immobilization of Abs & Functionalization	Label	Time	Range culture	Food	
✓ Target bacteria binding aptamers are adsorbed on the surface of unmodified AuNPs to capture target bacteria, and the detection was accomplished by target bacteria-induced aggregation of the Aptasensor which is associated with	Label free	20 min or less	10^5	PBS	[58]
✓ Two single-stranded DNA sequences were tested as recognition elements and compared. ✓ The aptamer capture probes were immobilized, with and without 6-mercapto-1-hexanol (MCH) on a gold electrode.	Label free	-	10^{-7}–2×10^{-6} M	Water	[59]
✓ the target *E. coli* was captured by antibody-conjugated magnetic beads. ✓ the RNA aptamers were bound to the surface of captured *E. coli* in a sandwich way. ✓ the heat-released aptamers were amplified by using real-time reverse-transcriptase-PCR (RT-PCR)	-	Real time	from 10^1 to 10^7 (cfu/ml)	PBS	[60]
✓ the aptamer for *Escherichia coli* O111 was immobilized on a gold electrode by hybridization with the capture probe anchored on the electrode surface through Au-thiol binding.	-	3.5 h	112 & 305	PBS and Milk	[61]

Table 6: Aptasensors intended for the detection of *E. coli*.

potential supplement for direct, label-free detection of bio-molecules with their superior ultra-high sensitivity and scalability and low-power consumption, low-fabrication cost, and excellent portability. Bio-FETs are semiconductor-based structures functionalized with suitable bio-receptors, which detect bimolecular interactions in a label-free potentiometric fashion and with great sensitivity. In conventional bio-FETs, the surface of the gate dielectric layer, as a sensitive layer, is functionalized by receptors for selectively capturing target molecules. This causes an electrostatic gating effect when the target molecules are captured. The sensitive component can be a functionalized Nano ribbon, nanotube or Nano sheet; the latter two cases being the focus of the researchers. Since these 1D and 2D materials have inherently small body dimensions compared to 3D materials, when they are applied to transistor-like devices, the carriers in these materials are expected to be better modulated by electrostatic effects, such as gate electric-field in the transistor and positively/negatively charged target molecules in the biosensor. In particular, graphene and carbon nanotube-based FETs (GFETs and CNT-FETs) present exciting and bright prospects for sensing applications due to their significantly higher sensitivity and stronger selectivity. For this reason, this review scrutinizes a selection of important and recent topics pertinent to GFETs and CNT-FETs and their application as a biosensor in the detection of *E. coli*.

Carbon-nanotube FETs (CNT-FETs)

Carbon-based nanomaterials such as CNTs, as an interesting transducer, have allegedly enhanced the performance of biosensors [64-73]. On the one hand, these nanomaterials exhibit particular electrical and physical properties. On the other hand, highly porous 3D networks on their surface increase the density of receptors that are immobilized on the surface. Researchers then piece together how these features correlate to increase sensitivity, which some of the more significant findings are highlighted hereafter.

In 2013, a CNT-FET biosensor was fabricated with the enrichment SWNTs for *E. coli* O157:H7 detection by Zhang et al. [74]. They reported a simple, scalable way to enrich semiconducting SWNTs by using an HNO_3/H_2SO_4 solution. The CNT channels were modified by the linker PASE, which plays an important role in immobilizing nanotubes and antibodies. Since the special structure of PASE is composed of two functional groups, pyrene and CFSE, Pyrene moiety could be functionalized with the SWNTs by π–π stacking and succinimidyl ester could react with $-NH_2$ in an antibody to be a covalent bond.

In terms of electrical properties of the device, I-V measurement indicated that CNT-FET had p-type characteristics in the blank PBS buffer. Finally, the time dependence of the resistance of CNT-FET after the introduction of O157:H7 at a different concentration into antibody CNT-FET has been investigated; resistance increases sharply to the maximum after it is dropped into the solution. Then it decreases rapidly in around 50 sec to a relatively stable level.

Subramanian et al. have described an electronic platform to detect very small amounts of genomic DNA from bacteria and without the need for PCR amplification and molecular labeling, as can be observed in Figure 3 [75]. This work has highlighted the detection sensitivity and influence of this biosensor without the stringent requirement of DNA sample preparation. This system uses CNT-FET arrays whose electrical properties are affected by instant electrical charges localized on their active regions, since the DNA is intrinsically charged from its phosphate backbone.

A new 45-mer probe specific to *E. coli* O157:H7 has been used along with the protocols for immobilization, hybridization, dehybridization, and blanking, which are essential for proper operation and accurate analysis of results. These results are consistent with negative charge accumulation on the gold gate surface for probe immobilization and hybridization, which in turn is measurable as a positive shift in Vth, while the dehybridization reduces the surface charges. This shift of the threshold voltage has a relation with the bound surface charges given by the following equation:

$$\Delta V_{th} = \frac{\Delta\sigma_{DNA}}{C_D} \quad (1)$$

Where, Δσ_DNA the added surface charge per unit area on the transistor and_C_D where is the effective capacitance per unit area is arising from the double layer the screening effect of the mobile ions around the bound charges Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

This detection methodology relies on the unique properties of SWCNTs to increase the sensing surface area [76]. In 2014 a 2 × 2 multi-crossbar junction sensing array including gold-tungsten wires (50 μm diameter) coated with polyethylenimine (PEI) and SWCNTs was fabricated for the detection of *Escherichia coli* K-12, [77]. The crossbar junction was functionalized with streptavidin and biotinylated antibodies to improve specificity towards targeted cells. The electrical current changes after bioaffinity reactions between bacterial cells and antibodies on the SWCNT surface. In this study, a linear relationship (R_2=0.973) was reported between the changes in current and concentrations of bacterial suspension in the range of 10^2–10^5 CFU/mL.

Graphene-based FET (G-FET)

Graphene sheet, a monolayer of carbon atoms packed into a two-

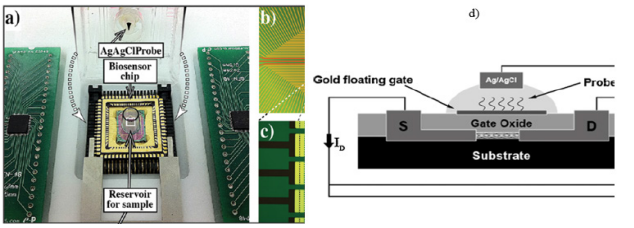

Figure 3: Platform for genomic DNA detection (Subramanian et al.,): (a-c) A biosensor chip, where the dark regions are the metal pattern, the intermediate contrast (green) regions are the semiconductors with an oxide passivation layer and the bright regions (gold) are the gold coated gate active areas upon which the gold oligomers are immobilized; (d) Principle of operation. When target DNA is captured at the gold floating gate, the curve representing the drain-source current (ID) *versus* gate voltage (VGS) shifts by an amount, Vth, commensurate with the amount of extra charges that have been captured [77].

dimensional honeycomb lattice with unique electrical, physical, and optical properties, is considered to be a promising semiconducting material for FETs [78-83]. The intrinsic Graphene, as a zero-gap semiconductor, has remarkably high-electron mobility (about 100 times greater than that of silicon), making it ideal and efficient for electronic devices, energy storage, atomic-scale and high-speed chemical/biological sensors. Since Graphene can be prepared cost effectively by reducing Graphene oxide (GO), the thermally reduced GO (TRGO)-based biosensors have been developed with advantages such as tunable electronic properties (ambipolar, n- or p-type semiconducting behavior), simple device structure, and label-free detection, some of which have been considered below.

With regards to this, Chang et al. [84] have demonstrated highly sensitive and selective FET sensors for the detection of *E. coli* bacteria using thermally reduced monolayer GO (TRMGO) sheets as semiconducting channels. At first, the GO sheets are assembled on the aminoethanethiol (AET)-functionalized gold (Au) electrodes through electrostatic interactions assisted with ultrasonic (Figure 4). Then, anti *E. coli* antibodies, as selective receptors for the detection of *E. coli* cells, have been immobilized on the GO surface through covalent bonding with Au nanoparticles (AuNP). The TRMGO FET device shows stability and high sensitivity to E. coli cells with a concentration as low as 10 CFU/mL. The conductibility of the devices continued to rise with increasing concentrations of *E. coli* cells. The dynamic response of the device has been measured with the specific binding such that the conductance of the device increased correspondingly with the insertion of the E. coli cell solution and the current change in the device was around 1.1% with the introduction of 10 CFU/mL.

As the second device introduced in this section, Lui et al. [85] have demonstrated a simple and selective methodology for the detection of gram-negative bacteria, *E. coli*, that outperformed other tested carbon nanomaterials. The detection method consists of exploiting interactions between Magainin I and gram-negative bacteria [86] and transducing those interactions into conductance changes using (holey reduced Graphene oxide) hRGO-based FET devices The results show that hRGO affords a rich chemistry that facilitates the functionalization of highly sensitive sensors while retaining the useful electronic properties.

Additionally, in order to examine the efficiency of hRGO versus other carbon nanomaterials, RGO, commercially available pristine SWNTs (pSWNTs), and oxidized SWCNTs (oSWNTs) have also been employed as the transducer element in FET devices to detect bacteria (Figure 5). For RGO and pSWNTs, this low response may be attributed to the amount of oxygen functionality (i.e., carboxyl groups) available for coupling. At low concentrations of this functional group, minimal antimicrobial peptides (AMP) would be bound, which would result in insufficient binding of the bacteria. The low efficiency of oSWNTs, which underperformed all other samples, can be attributed to the availability of the oxygen content as well as the loss of the electronic efficiency from oxidization.

The final case has been allocated to a Graphene-based FET real-time detector of the target bacteria *E. coli* K12 in food and water in order to guarantee food safety [87]. After the device fabrication process, the Graphene-based FET sensor is functionalized as ssummarized as follows Figure 6: a) A solution of 6 mM 1-pyrenebutanoic acid succinimidyl ester (1-PBS) in dimethylformamide (DMF) is prepared. Then the device is incubated with this 6mM1-PBSE (Sigma-Aldrich, 457078) dimethylformamide (DMF, Sigma-Aldrich, D4551) solution for 2 hours at room temperature; b) A 50 ppm anti-*E. coli* O + *E. coli* K antibody (Abcam 33604) in DI water solution is prepared; c) The microchip is incubated with 0.1 Methanolamine (pH 9.0) for 1 hour; d) The device is incubated with 0.1% Tween 20. After the *E. coli* K12 molecules with negative charges attach to the sensor surface, the bacteria induce holes in the Graphene channel, increasing the bias

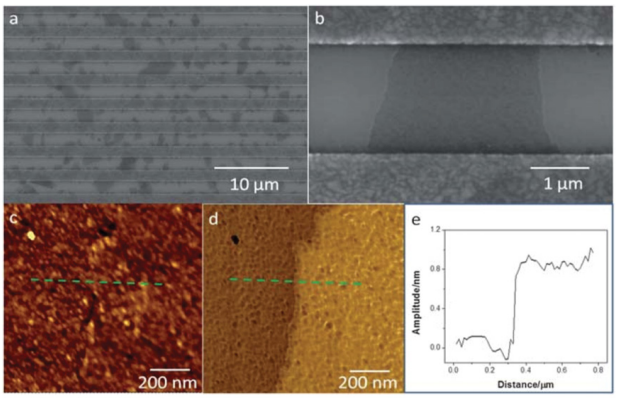

Figure 4: TRMGO sheets across the electrode gaps: (a and b) SEM images of AFM data (tapping mode) on a silicon wafer, (c) height and (d) phase images of the same zone at a cross-sectional area (dashed line indicates a scanning trace), (e) Height profile obtained by scanning from a bare silicon wafer to TRMGO [86].

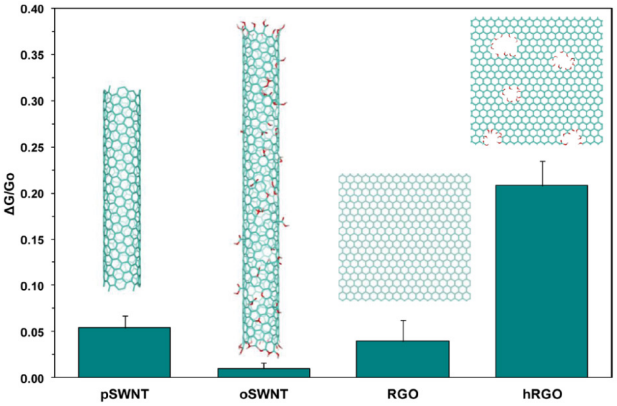

Figure 5: Comparison of the mean normalized responses (Vg = −0.5 V) of four Magainin I functionalized carbon nanomaterials to 107cfu/mL *E. coli*. Averaged from four devices; the error bars represent 1 standard deviation [88].

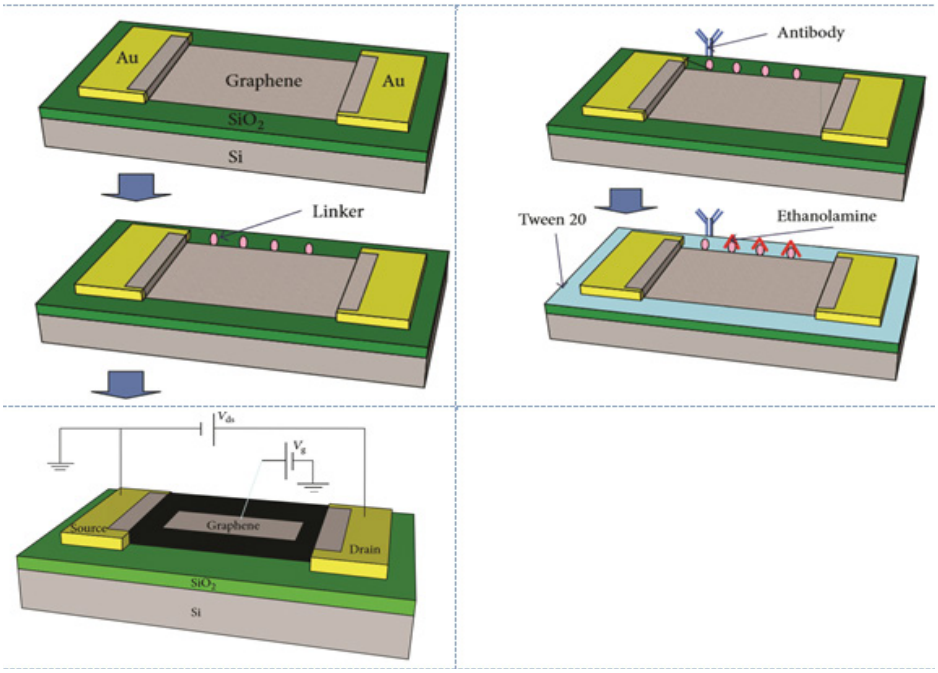

Figure 6: Solution using gate Graphene-based FET. Gate voltage (Vg) is applied to the solution inside the recording chamber. The chosen linker is 1-pyrenebutanoicacid succinimidyl ester; the antibody is anti-*E. coli* O and K antibody (Abcam 33604) [89].

current of Graphene FET due to the increment of carrier numbers. The corresponding relationship between bacteria concentration and carrier density could be found.

Taking into account some limitations of the G-FET and CNT-FET, such as device sensitivity due to the Debye–Hükel phenomenon and limited surface area, is fundamental in developing improved bioelectronics for applications in the clinical setting. The Debye-Hükel phenomenon decreases the Debye-screening length, and as a result reduces the sensitivity outside of this length. However, significant efforts have focused on bypassing this issue by alternating the nucleic acid-based sensors, aptasensors, and antigen-binding fragment (Fab) modified G-FETs and CNT-FETs. Using aptamers and Fabs as bioreceptors declines the distance of the interaction between receptors and target molecules from 10-15 nm to 3-5 nm. The Debye-screening length for the 0.01×PBS solution is 7.4 nm. Although Graphene has an inherently large area, it was reported that this feature could be further improved, and has resulted in increasing the sensitivity. This was possible by decorating the G-FET surface with metal nanoparticles, increasing the binding sites for the bio-recognition element, and therefore the target analyte. In 2017, Wu et al. reported bio sensing using G-FETs with the aid of pyrene-tagged DNA aptamers, which exhibit excellent selectivity, affinity, and stability for *E. coli* detection. The aptamer is employed as the sensing probe due to its advantages such as high stability and high affinity toward small molecules and even whole cells [81].

The ambipolar characteristic is a unique V-shaped transfer curve for graphene, which simultaneously exhibits the transfer feature of p-type and n-type transistors. In order to evaluate the interaction between biomaterials and graphene from the perspective of its ambipolar characteristic, Mulyana et al. [88] investigated the alteration in ambipolarity of G-FET after the adsorption of *E. coli* bacteria onto its graphene layer. After the adsorption of *E. coli*, due to the negative charge of the *E. coli* cells, a positive shift was observed in the ambipolar curve. A significant advantage of this study was no decrease in the electron mobility or conductivity of the G-FET, confirming that *E. coli* cells were only physically adsorbed onto the graphene surface without any damage to the graphene lattice.

In most scientific fields, modeling is a powerful method that can help predict the performance of the device. Recently, Wu et al. modeled and simulated a G-FET with COMSOL Multiphysics where they used to study the motion of *E. coli* cells in electrolytes and the surface charge induced by *E. coli* on the graphene [89]. The results show that the sensing probe size is a key parameter affecting the surface charge of graphene The graphene-bacteria distance, defined by the size of the sensing probe, is found to play a key role in improving the sensing performance of the biosensors since it leads to more efficient induced surface charge and a resultant larger electrical response. Smaller graphene-bacteria distances and higher bacterial concentrations yield larger changes of source-drain current of the biosensor.

In other words, in terms of electrical properties, the results show that the power consumption of these sensors is very high because they create off-currents. However, a new generation of transistors, such as multi-gate transistors, improves the short channel effects. Although Graphene has many interesting features compared to other semiconductor technologies, the majority of these characteristics measured in G-FET and CNT-FET sensors depend on the quality of the fabricated samples based on a prototyping procedure. Therefore, it is difficult to obtain this in a mass-scale manufacturing process.

To solve these limitations, CMOS technology is proposed, which is a powerful fabrication technology for biosensor implementation as the case for both system-and lab-on-chip potentials [90-93]. Moreover, this technology has the ability to scale down with a nanometer-scaled feature size, interacting in most biosensing schemes. The cost-effective and mass production of CMOS provides an opportunity to design

scalable sensors as well as the implementation of a sensor array for the simultaneous detection of analytes. However, the materials used in CMOS technology are not biocompatible, so it is necessary to do some post-process steps. In other words, the connections to the external components for readout driver or powering a chip should be protected from the chip as well. For an accurate investigation of CMOS-based sensors to detect *E. coli*, the characteristics of main devices have been listed in Table 6. Potentiometric sensors, which measure pH changes, meet the needs for low sensitivity and cost-effectiveness. Giang et al. developed a high-sensitivity ion-sensitive FET sensor which was massively fabricated in a standard 65-nm CMOS process [94-99]. It was amplified to 123.8mV/pH with a 0.01 pH resolution, which greatly exceeded 6.3 mV/pH observed in a traditional source-follower based readout structure. This sensing system was applied to *E. coli* detection with densities ranging from 14 to 140 CFU/mL.

Conclusions

With regards to the existing challenges to improve the properties of the biosensors, there has been a serious attempt to put forward new methods to complement laboratories-based ones In this way, nanotechnology (composed of nano-materials and nano-devices) has advanced as a new discipline to diagnose and manage health problems all over the world. The development of biosensors mostly relies on sensitivity, specificity, non-toxicity, small molecule detection and cost-effectiveness. These characteristics will eventually address critical parameters required and related to major limitations of these detection methods. Overall, an appropriate combination of these methods may conduct to successful development of expected biosensors in the modern era. Ultimately, we have discussed the use of CMOS technology for biosensing with a special focus on the efforts being invested into the combination of existing CMOS technology and nanomaterials such as carbon nanotubes, and Graphene based devices. The findings contend that CNT-FETs and G-FETs can be a promising technology for a label-free, rapid, precise portable analysis suitable for molecular screening of pathogens and diagnostics of genetic-based disorders. According to the consequences presented earlier, the conclusion can be drawn that in contrast to the aforementioned advantages, CNT-FET and G-FET have some drawbacks. These restrictions account for a new generation of FETs, including multi-gate transistors, which have recently drawn some attention as a promising device in biosensing. It is noteworthy that multi-Gate FETs with much better control on the channel conduction and increasing surface for immobilizing receptors, will lead to improvements in sensitivity and accuracy. Currently, based on attempts in various fields of bioscience, researchers express that they tend to achieve comprehensive assay tools such as lab-on-a-chip (LoC based platforms).

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