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DNA hybridisation sensors for product authentication and tracing: State of the art and challenges

Gloria Ntombenhle Hlongwane[a,b,e], David Dodoo-Arhin[a,c], Daniel Wamwangi[d], Michael Olawale Daramola[b], Kapil Moothi[e,*], Sunny Esayegbemu Iyuke[b]

[a] African Materials Science and Engineering Network (A Carnegie-IAS RISE Network), South Africa
[b] School of Chemical and Metallurgical Engineering, Faculty of Engineering and the Built Environment, University of the Witwatersrand, Wits, 2050, Johannesburg, South Africa
[c] Department of Materials Science and Engineering, School of Engineering Sciences, University of Ghana, P.O. Box Lg 77, Legon-Accra, Ghana
[d] School of Physics, Faculty of Science, University of the Witwatersrand, Wits, 2050, Johannesburg, South Africa
[e] Department of Chemical Engineering, Faculty of Engineering and the Built Environment, University of Johannesburg, Doornfontein, 2028, Johannesburg, South Africa

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ABSTRACT

The wide use of biotechnology applications in bioprocesses such as the food and beverages industry, pharmaceuticals, and medical diagnostics has led to not only the invention of innovative products but also resulted in consumer and environmental concerns over the safety of biotechnology-derived products. Controlling and monitoring the quality and reliability of biotechnology-derived products is a challenge. Current tracking and tracing systems such as barcode labels and radio frequency identification systems track the location of products from primary manufactures and/or producers throughout globalised distribution channels. However, when it comes to product authentication and tracing, simply knowing the location of the product in the supply chain is not sufficient. DNA hybridisation sensors allows for a holistic approach into product authentication and tracing in that they enable the attribution of active ingredients in biotechnology-derived products to their source. In this article, the state-of-the-art of DNA hybridisation sensors, with a focus on the application of graphene as the backbone, for product authentication and tracing is reviewed. Candidate DNA biocompatible materials, properties and transduction schemes that enable detection of DNA are covered in the discussion. Limitations and challenges of the use of DNA biosensing technologies in real-life environmental, biomedical and industrial fields as opposed to clean-cut laboratory conditions are also enumerated. By considering experimental research versus reality, this article outlines and highlights research needed to overcome commercialisation barriers faced by DNA biosensing technologies. In addition, the content is thought-provoking to facilitate development of cutting edge research activities in the field.

1. Introduction

1.1. Consumer expectation

Over the years biotechnology applications have been widely used in bioprocesses in food and beverages, pharmaceutical, medical diagnostics and wastewater treatment industries (Kingsbury, 1987; Richards, 1991; Ludwig et al., 1995; Jobling and Gill, 2004). Since biological processes are complex and dynamic with continuously changing physicochemical conditions in order to ensure reliability and obtain good quality products, the bioprocess needs to be controlled and monitored (Carloni and Turner, 2011; Schügerl, 2001). This is particularly important in bioprocesses used in the food and beverages and pharmaceutical industry in order to assure the consumer/patient of the quality and safety of the products produced.

Continual occurrences of food scares and scandals have become a battle that requires the world's attention. Consequently, fields involved in product authentication are burdened with the responsibility of preventing possible, newly emerging, and pre-existing product scares and scandals. Due to consumer awareness of these incessant occurrences of food borne outbreaks/scandals, consumers have expectations (Berg, 2004; Chambers and Melkonyan, 2013). Inasmuch as a consumer yearns for assured safety and authenticity in a product prior and subsequent to its release to the supply chain, assurance in time of crisis is also required by the public. That is, should there be any; (a) unexpected case of a scare and/or scandal post entry of the product in the supply

* Corresponding author.
E-mail address: kmoothi@uj.ac.za (K. Moothi).

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chain, or (b) a product is found to contain unauthorised components after it was assessed as safe, the public requires assurance that the product or product component of concern will be rapidly detected, traced and attributed to the source before it spreads and becomes a basis of panic to the public (Angulo and Gil, 2007; Verbeke and Ward, 2006; Zach et al., 2012). Therefore, it is the consumer's expectation that post-marketing product safety assessment surveillance is treated with importance that is equivalent to that placed on pre-market evaluation of potential risks (Schilter and Constable, 2002).

Recognising this need, in 2003 a Process Analytical Technology (PAT) initiative was launched by the United States' Food and Drug Administration (FDA) (Hinz, 2006). PAT is aimed at managing and controlling product quality from the raw materials throughout the production line to the final product using novel advanced analytical process techniques. The PAT framework encourages the subsequent use of real-time information obtained regarding the critical quality attributes product information obtained through monitoring and control process to authenticate and ensure product quality (Hinz, 2006; Junker and Wang, 2006).

1.2. Product authenticity

An authentic product is defined as a product whose compositional integrity concurs with the product's provenance and process of production as specified on the product's name, brand and ingredients (Dean et al., 2006; Murphy et al., 2010; Robinson and Clifford, 2012). Product authentication involves the classification and analytical discrimination of authentic products from non-authentic samples. In this regard, the following have been explicitly addressed in literature:

- The reduction of product borne incidences through strategic risk management tools and product safety regulation systems in the production chain (Walls and Buchanan, 2005).
- Implications that different product scandals have on the integrity of product safety regulation systems (Pei et al., 2011) and potential effect they could have the trade (Song and Chen, 2010; Yapp and Fairman, 2006).
- The development of novel methods of authenticating different products (Jaakola et al., 2010; Popping, 2002; Primrose et al., 2010; Reid et al., 2006).

Since products are classified by stringent parameters that describe traits relating to the origin and background of the product. Authentication of products is vigorous and often times involves the verification of legitimacy of claims made by the manufacturers about the composition and purity of the product in question. Therefore, testing of products strongly relies heavily on the use of technological and analytical techniques to critically discriminate products into their respective categories.

2. Analysis of product samples

2.1. Technology based techniques

Technology in product authentication is used to discriminate samples through innovative tracking and tracing systems. These technologies range from radio frequency identification (RFID) systems to barcode labels. As long as the tag is on the product's package, these systems will automatically document in real-time, information about the flow of products in the supply chain and its movement in globalised distribution channels (Bardaki et al., 2011; Hong et al., 2011). However, it is not sufficient to only have information about the location of the product in the supply chain. For a comprehensive post-marketing product safety assessment surveillance, information about the components of the product needs to be collected and validated. Irrespective of the products' location, the characteristics of its constituents have to be ascribed back to their source (Kruse, 1999; Loureiro and Umberger, 2007). Therefore, the demand for sensitive analytical techniques/devices that are reliable, cheap, fast, and can be used on-site is growing (Ahmed, 2002). It is essential that these on-field analytical techniques/devices allow for;

- Authentication of the product through specific identification of traits of its different components, and
- Direct traceability by communicating of background information about the product's specific raw material.

Fields involved in product authentication are aware that an accentuation of post-marketing product safety assessment surveillance to importance that is equivalent to that of pre-market evaluation of potential risk could potentially provide a holistic view into the authentication of products. As a result, several sophisticated analytical techniques commonly referred to as conventional techniques have been developed and proposed as highly crucial methods of monitoring the authenticity and quality of products. Chromatography and Spectroscopy are examples of these highly recommended techniques (Costa et al., 2012; Lüthy, 1999). However, ambiguous results can be obtained using these techniques as similar products can be produced by different organisms (Costa et al., 2012; Lüthy, 1999). To authenticate products unambiguously, particularly plant and animal based products, analytical techniques based on qualitative and/or quantitative analysis of foreign and characteristic traits specific to the source-organism are attractive alternatives. Therefore, Cellular and Molecular Biology techniques which are either protein- or DNA-based are the preferred alternatives when it comes to checking the authenticity of products derived from plants and/or animals (Ahmed, 2002; Lüthy, 1999; Shrestha et al., 2010).

2.2. Cellular and molecular biology techniques

2.2.1. Protein-based techniques

Protein-based techniques are of either electrophoretic and immunoassay origin (Lüthy, 1999). The most popular protein-based techniques used to detect proteins are western blot and enzyme-linked immunosorbent essay (ELISA). Their subjectivity is reduced through automation (Dooley, 1994). However, the reliability of the techniques is restricted by the inherent low threshold levels of proteins. Proteins are thermodynamically unstable and heat liable (Costa et al., 2012; Lüthy, 1999; Shrestha et al., 2010). Moreover, protein-based techniques can be ambiguous since organisms of different species can share phenotypic properties. The probability of this occurring is increased by genetic diversity. For example, genes with small differences in nucleotide base sequences can code for proteins with identical amino acid sequences thus resulting in proteins coded for by different genes possessing identical structures and functions (Dooley, 1994; Lüthy, 1999). In such cases, it becomes difficulty if not impossible to discriminate proteins produced by the target organism from those of a non-targeted organism. Therefore, analytical techniques that are based on targets whose detection is independent of gene expression are more attractive (Dooley, 1994).

2.2.2. Nucleic acid-based techniques

Nucleic acid-based analytical techniques are independent of gene expression. These techniques recognise nucleic acids as unique molecules. The presence of nucleic acids in products is taken advantage of in product authenticity investigations. The application of nucleic acids is mainly established in basic research. The use of nucleic acids in analytical techniques allows for exploitation of species or genus specific genotypic signatures of any organism with detectable genomic material. Genotypic signatures range from a promoter or terminator, to a gene itself, transgenic or not. Detection of genotypic signatures is used for in various fields including environmental and health surveillance.

Surveillance of this calibre is practically achieved through a probe, a defined nucleic acid fragment. A nucleic acid probe is an identified single stranded sequence of nucleotide bases. Through specific and complementary binding to a target sequence of nucleotides, it is used to detect and identify target nucleic acids in a mixture of nucleic acids (Richards, 1991; Wetmur, 1991; and Wolcott, 1992). Since all organisms theoretically have unique sequence of nucleotide bases, probes targeted at recognising a specific nucleic acid region in the nucleotide base sequences of any living organism can be produced. The target sequence of nucleotides is usually of recognisable genotypic properties unique to genus or species. Nucleic acid probes can either be Deoxyribonucleic acid (DNA) or Ribonucleic acid (RNA). RNA requires gene expression to occur, consequently DNA is more attractive as it is independent of gene expression.

DNA-based analytical techniques bring to light the obscure link between product safety, quality and genomic signatures (Lüthy, 1999). The DNA thermo-stability comparative to that of proteins reinforces DNA's suitability in authentication methods. Furthermore, DNA is highly selective and specific thus making it an effective target in DNA-based analytical techniques that authenticate plant and animal based products. Using DNA, genetically modified organisms can be reliably discriminated from their non-genetically modified counterparts (Costa et al., 2012; Lüthy, 1999).

To date, DNA-based analytical technique that are most established, sensitive, qualitative, quantitative, and that allow for accurate DNA detection, are based on real time polymerase chain reactions (PCR). DNA sequences of target genes that uniquely specific to an organism can be recognised through PCR-based techniques (Davison and Bertheau, 2007; Hahn et al., 2005). These involve amplification of trace concentrations of DNA in addition to specific identification of DNA sequences using primers (Davison and Bertheau, 2007). Southern blot analysis, gel electrophoresis, commercial DNA sequencing, and restriction digestion and analysis are among a few on a vast list of laborious and expensive techniques through which identification of DNA sequences is achieved. Furthermore, well-equipped laboratories with experienced and trained investigators are required to optimise results from PCR-based techniques (Karamollaoğlu et al., 2009; Passamano and Pighini, 2006; Wu et al., 2009). Without a doubt, DNA-analysis for purposes ranging from healthcare to food safety, was revolutionised by the development of PCR (Hahn et al., 2005; Lüthy, 1999). However, the development of innovative high-throughput, miniaturized, cheap and extremely rapid on-field analytical devices that are easily operated by individuals without any laboratory training or experience is equally if not more revolutionary (Hahn et al., 2005; Karamollaoğlu et al., 2009; Nugen and Baeumner, 2008; Passamano and Pighini, 2006). These analytical devices are biosensors and bioelectronics.

2.3. Biosensing technologies

The first mention and illustration of a form of a biosensing technology was by Professor Leland C. Clark in 1956. Despite this early illustration of such a technology, the definition and proof of concept of Biosensors occurred only in the 1970s (Clark and Lyons, 1962; Mascini, 2006; Vigneshvar et al., 2016). From a Scopus bibliometric analysis of literature related to biosensors depicted in Fig. 1, the number of publications on biosensors has increased tremendously over the last 41 years. From this bibliometric data it is also observed that research in the field of biosensors peaked in the year 2015 with work published in a wide range of scientific fields (Fig. 2).

Biosensors are described at their most basic form as self-contained analytical devices that consist of a support material with a bioreceptor/probe bound to it. The bioreceptor/probe is immobilised as a bio-recognition layer onto the support. Binding of the bioreceptors onto the supports is made possible by the biocompatible nature of the support materials. This bio-recognition layer is responsible for the detection and specific binding of the target analyte while a transducer converts the corresponding biological reaction due to the interaction between the bioreceptor in the bio-recognition layer and its specific target analyte into a detectable and measurable signal which can be used to qualitatively screen for the target analyte (Thévenot et al., 2001; Vo-Dinh, 2004; Mascini, 2006; Wang, 1999). Therefore, the basic working principal of biosensing devices is intimate coupling of bioreceptors and biocompatible support materials that transduce the bio-recognition even into various signals (Wang, 2000). In the following sections of this work, recent advances and trends in the areas of bioreceptors, biocompatible materials and different transduction methods used in biosensors will be reviewed.

2.3.1. Bioreceptors

Biosensors are classified based on the type of bioreceptor, support and subsequent nature of the biological recognition event. They are categorised into affinity- or biocatalytic-based biosensors. Components of organisms ranging from proteins and nucleic acid to an entire microorganism are used as bioreceptors form different kinds of bio-recognition layers. Biocatalytic sensors primarily utilise immobilised proteins as bioreceptors. On the other hand, nucleic acids and antibodies are utilised as bioreceptors in affinity-based biosensors (Thévenot et al., 2001; Vo-Dinh, 2004; Wang, 1999). Enzymes are also used as bioreceptors but typically not as actual bioreceptor instead as a label (Velusamy et al., 2010). Due to the aforementioned DNA stability, independence of DNA to gene expression and DNA self-recognition properties, bio-recognition layers composed of DNA have attracted attention in modern microarray and biosensing technologies. In spite of the many applications that biosensors can be designed for in various platforms (Nugen and Baeumner, 2008), growing interest in fundamental research and commercial development of biosensing technologies is on affinity-based biosensors that utilise nucleic acids, in particular DNA (Teles and Fonseca, 2008; Wang et al., 2013). DNA biosensors have revolutionised genetic analysis before the 21st century, and developments of DNA biosensors has been rising since as depicted by the number of publishing in this subject over years in Fig. 3 (Wang, 2000).

In these types of sensors, DNA hybridisation is the biological recognition event hence the term DNA hybridisation biosensors (Fig. 4). Immobilisation of a single-stranded DNA probe onto support materials such as silicon (Wang et al., 2012) gold (Lockett et al., 2008), and graphene (Du et al., 2012), enables sequence specific detection of DNA hybridisation by these sensors.

2.3.1.1. Strategy in designing DNA probes. To date, there is no reported unified approach to follow when designing a probe of interest especially for application in biosensing technologies. Nevertheless, in designing an ideal probe, the only reported requirements that need consideration are that: (1) probe nucleic acids hybridises specifically and selectively to the target sequence nucleic acids; (2) probe must not self-hybridise nor should the probe hybridise to non-target sequence nucleic acids in a sample mixture of nucleic acids and; (3) the non-target cells should not have the targeted sequence of nucleic acids (Abd-Elsalam, 2003). The function of the target sequence nucleic acids or the identity of the target is not essential, provided that the choice of target sequence is of significance to the research study in question. Depending on the intended application of the device a probe can be designed to identify and bind to: nucleic acids specific to a genera, species, or species of organisms, and conserved gene or conserved fragment of a gene in a species (Kingsbury, 1987; Wolcott, 1992).

In general, a probe is a short single-stranded (ss) strand of DNA with lengths ranging from 10 to 10000 base pairs (bp). A minimum of 20 bp of the nucleotide bases are required for statistical uniqueness (Wolcott, 1992). The recommended length of a probe for biosensor applications ranges from 15 to 50 bp (Gooding, 2002), while the most common probes used in electrochemical sensors is 15–40 bp (Wolcott, 1992; Wang, 1999). This recommendation is supported by the fact that short

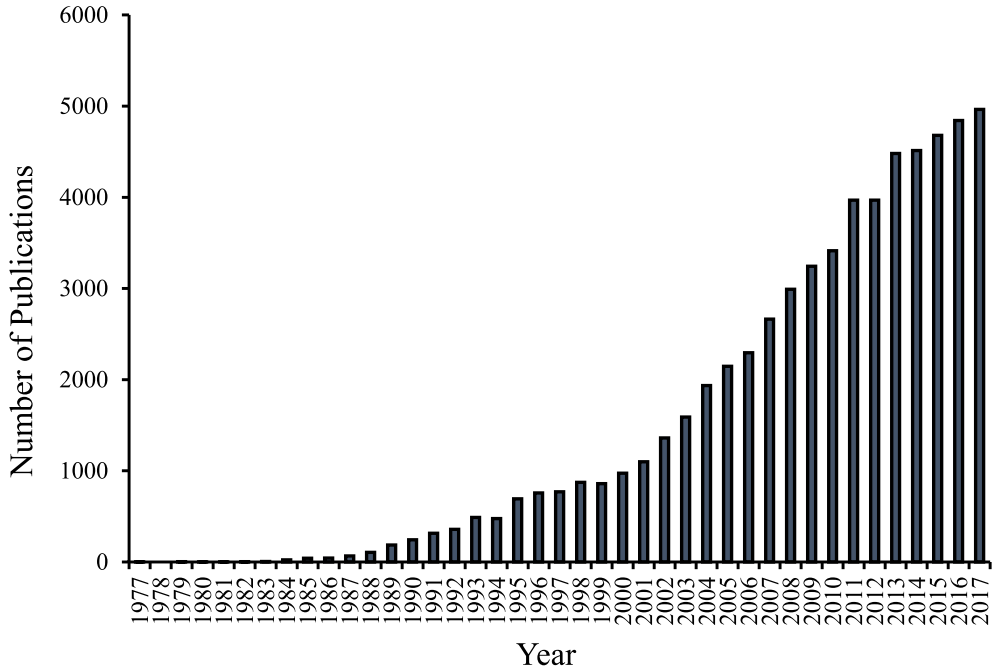

Fig. 1. Bibliometric survey analysis, for the year 1977–2017, using data provided in Scopus SciVerse of publications related referring to the keyword biosensor.

probes are effective in rapid stable hybridization with the target sequence at high rates than the longer probes (Wolcott, 1992). Furthermore, it has been shown that probes that are shorter than 15 bp lead to a reduction in sensor sensitivity, while probes with larger numbers of base pairs result in the lack of response by the sensor (Goda et al., 2013). It should be noted that the base composition of DNA probes does not necessarily have a significant influence on the sensitivity of the sensor but differences in base sequence could lead to variation in response signal thus providing the sensor its selectivity and specificity feature (Drummond et al., 2003). The sequence information of the probe can be derived using wide variety of bioinformatics tools (Abd-Elsalam, 2003) and produced using either cloning strategies or automated chemical synthesis of oligonucleotide. Automated chemical synthesis of oligonucleotide is the most convenient method of probe sequence production (Richards, 1991).

2.3.1.2. Principles of DNA. Since the description of the structure of DNA by Watson and Crick in 1953, unique properties of DNA have revolutionised both biological sciences and fields that find biological concepts valuable (Wolcott, 1992; Jobling and Gill, 2004). It is the ability of a single-stranded DNA (ssDNA) to form duplexes through hybridisation of ssDNA to another ssDNA of complementary nucleotide bases that makes application of DNA probes so prominent. To form probe-target duplexes, the same concept of hybridisation of complementary nucleotide bases (Fig. 5) to form the Watson and Crick' DNA coiled double helix structure is applied (Trevors, 1985;

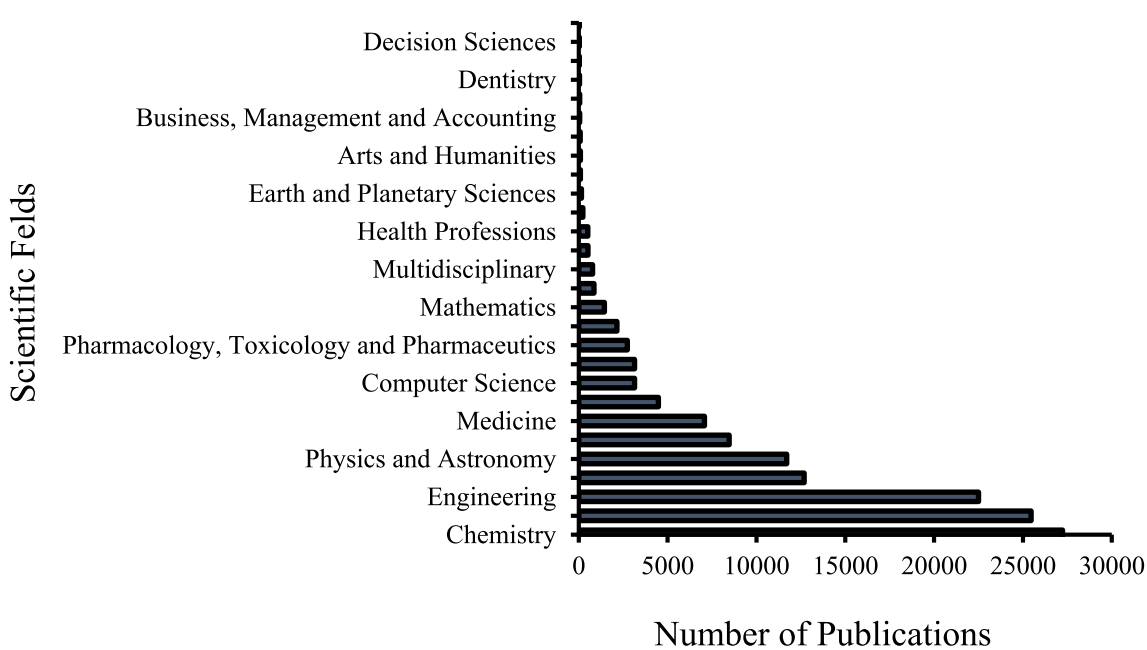

Fig. 2. Bibliometric survey analysis, for the year 1977–2017, using data provided in Scopus SciVerse of publications related to the keyword biosensor in various scientific fields.

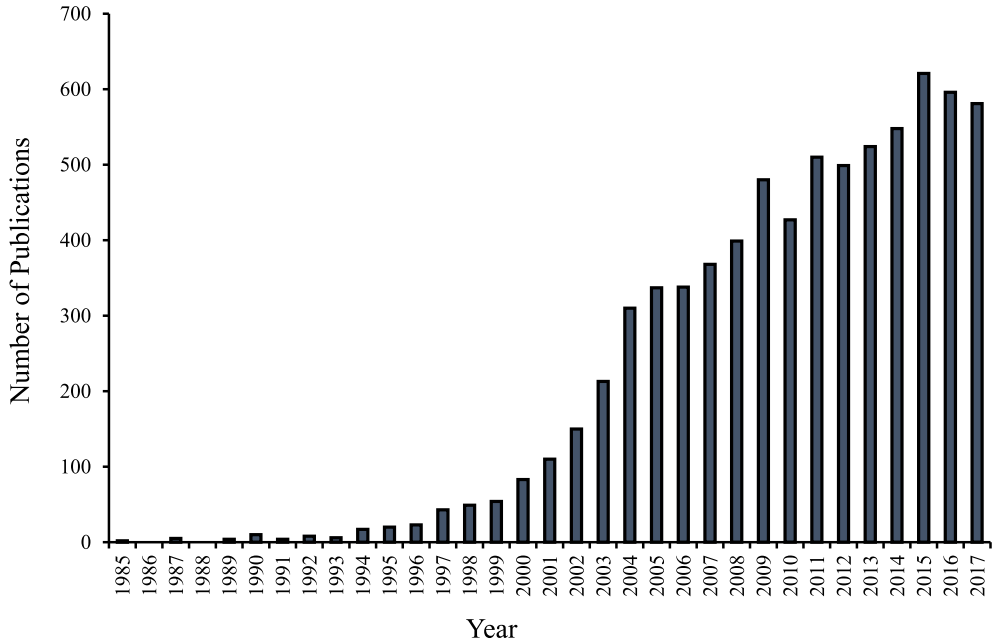

Fig. 3. Bibliometric survey analysis, for the year 1985–2017, using data provided in Scopus SciVerse of publications related to DNA biosensors.

Ludwig et al., 1995). Hybridisation is made possible due to the specific nature of DNA.

Specificity and selectivity of the probe to the target nucleotide base sequences is determined by hydrogen bond formation between the probe and target nucleotide base sequences in which two hydrogen bonds connect adenine (A) and thymine (T) and nucleotide bases, guanine (G) and cytosine (C) are connected by three hydrogen bonds (Wolcott, 1992). In DNA probe technology, these physical properties are manipulated in such a way that the probe or target is thermally or chemically separated if not initially single stranded (Wong and Passaro, 1990; Ludwig et al., 1995; Saccà and Niemeyer, 2012). Under appropriate hybridisation conditions a stable probe-target duplex is formed. Hybridisation is dependent on the temperature, pH, ionic strength, and DNA concentration (Kingsbury, 1987; Wong and Passaro, 1990; Dooley, 1994; Wang et al., 1997; Ludwig et al., 1995). Appropriately changing aforementioned conditions can reverse annealing of the probe and target to form the probe-target duplex to denaturing of the probe-target duplex (separation of the probe form target) or vice versa (Dooley, 1994; Gao et al., 2006; Dandy et al., 2007; Fiche et al., 2007). Probes can be used in several different hybridisation formats generally classified into those that employ a solid phase whereby the probe is attached to a solid support of some sort and liquid phase hybridisation reaction where neither probe or target are support bound (Richards, 1991).

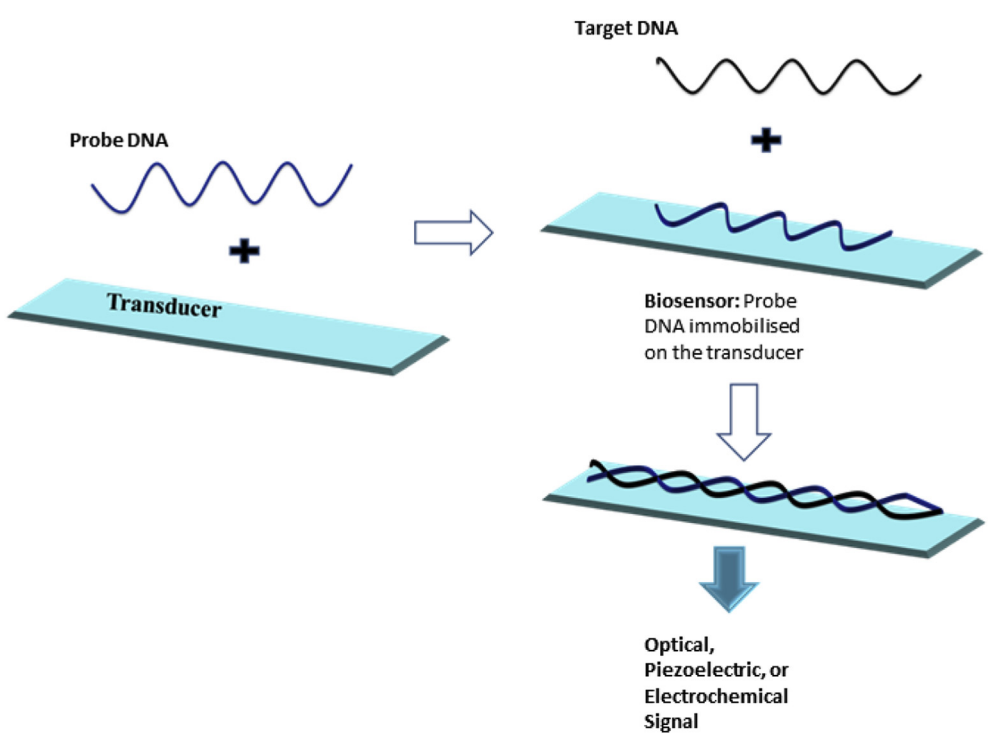

Fig. 4. Schematic illustration of the underlying concept in DNA hybridisation biosensors (Adapted from Du et al., 2012).

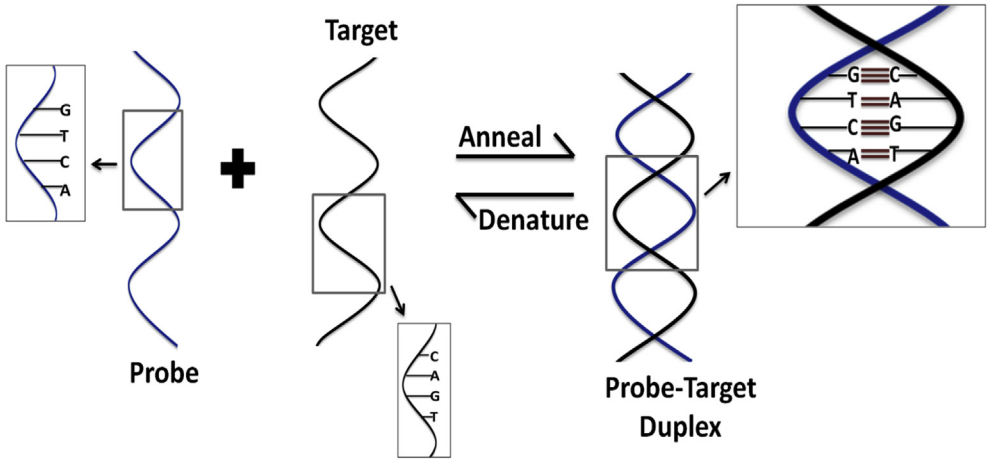

Fig. 5. Schematic representation of hybridisation of complementary nucleotide bases in a probe-target duplex. Nucleotide bases, adenine, cytosine, thymine and guanine are represented by letters A, C, T, and G, respectively (Adapted from Wolcott, 1992).

2.3.2. DNA biocompatible support materials

The semiconductor industry based on silicon has an already well-established microelectronics technologies linked to it. The recognition of traditional semiconductors such as silicon as potential support material in modern DNA microarray and biosensing technologies simply takes advantage of these existing microelectronic technologies. Moreover, the transition of silicon into a DNA immobilisation substrate is made possible by its flexible surface chemistry, great optical and morphological properties (Wang et al., 2012).

Detection of DNA hybridisation has been successfully achieved using silicon. Generally in silicon-based DNA hybridisation sensors, DNA immobilisation is achieved through covalent chemisorption and/or biospecific affinity interactions of the DNA molecule onto functionalised silica substrates (Wang et al., 2012; Lee et al., 2013; Hoyle and Bowman, 2010). Covalent coupling and bioaffinity interactions tends to preserve the bioactivity of the DNA. To achieve such high affinity covalent coupling and bioaffinity interactions, modification of the DNA molecule prior to immobilisation on the substrate is required. Typically this involves the use of DNA oligonucleotides that are amine-modified oligonucleotide, Cy3-and Cy5-labelled oligonucleotide probes (Gifford et al., 2010; Hoyle and Bowman, 2010; Wang et al., 2012). This use of labels limits silica and silicon substrates to predominantly optical DNA hybridisation signal transduction monitoring and analysis systems (Lockett et al., 2008). Moreover, silicon-based transduction materials are prone to hydrolysis leading to bioreceptor displacement from the silicon surface (Vermeeren et al., 2009).

Recently, the exploration of nanoparticles as important component (s) of sensors has been steadily increasing (Merkoçi, 2010). Nano-scale platforms in biosensors allows for the development of novel signal detection and transduction technology and/or schemes (Fernandes et al., 2014). For example, Zhou and Zhou (2004), was able to achieve stability in aqueous electrolytes and organic solvents by developing unique core-shell silica nanoparticles that protect the fluorophore molecules in the core during DNA detection. The use of nano-scale materials in biosensor fabrication is permitted by the extraordinary changes in catalytic, magnetic, electrical and optical properties of these nanoparticles when interacting with various kinds of biomolecules (Merkoçi, 2012; Pérez-López, and Merkoçi, 2011). The development of novel DNA sensors has also witnessed promotions due to nanotechnology. The biocompatibility of nanoparticles with DNA not only promises superior sensing functionality but also assures an enhanced electron-transfer kinetics (Nadzirah et al., 2015). Herein, the main types of nanoparticles used in DNA sensing are outlined with greater emphasis placed on graphene and/or graphene related materials.

2.3.2.1. Metallic nanoparticles. A number of metallic nanoparticles such as gold (Dykman, and Khlebtsov, 2012), palladium (Chang et al., 2008), platinum (Gill et al., 2006), silver (Liu et al., 2006) nanoparticles, etc., have been studied as DNA biocompatible support materials. The most explored metallic nanoparticles in DNA sensors is gold. Unlike silica and silicon substrates, gold substrates are not limited to optical DNA hybridisation signal transduction monitoring and analysis systems (Lockett et al., 2008). Despites the fact that gold is chemically inert, DNA can be immobilised on bulk or nanoparticle gold surfaces through chemisorption and biospecific interactions that are compatible with other modes of signal transduction monitoring systems such as mass-based and/or electrochemical signal (Hahn et al., 2005; Karamollaoğlu et al., 2009; Kerman et al., 2003; Passamano and Pighini, 2006). Aspects ranging from synthesis, properties and application of gold nanoparticles as sensors for food safety screening have been recently reviewed by Chen et al. (2018). To avoid repetition of literature, other thorough information on the state of the use of gold nanoparticles in modern DNA sensing platforms and different DNA detection and transduction schemes using gold of nanoparticles can be obtained from recent reviews by Qin et al. (2018) and Saha et al. (2012), respectively. Initially, DNA functionalised platinum nanoparticles were mainly presented as favourable catalytic labels for the optical DNA detection systems (Gill et al., 2006). In such systems - quick, simple and highly specific/sensitive detection of DNA hybridisation down to a single base-pair mismatch at low concentrations using platinum nanoparticle-based DNA sensor has been successfully demonstrated (Kwon and Bard, 2012; Skotadis et al., 2016). The exploration of DNA functionalised platinum nanoparticles continues to widen into newer sensing strategies such as the motion-based biosensor constructed by Nguyen and Minteer, (2015). Overall, with the exception of gold nanoparticles, information on exploration and development of DNA sensors using mono-metallic nanoparticles is limited in literature. Metallic nanoparticles are usually exploited as part of composite nanoparticles such as bimetallic, trimetallic, and dichalcogenide nanomaterials in DNA sensing (Mandal et al., 2018). Accordingly, some metallic nanoparticles used in recent studies for DNA sensing as components of composite nanomaterials are discussed in Section 2.3.2.4 of this review.

2.3.2.2. Carbon-based nanoparticles. In recent years, carbon-based materials such as carbon nanotubes/carbon nanofibers, nanodiamonds/diamond-like carbon, and graphene (Allen et al., 2009; Geim and Novoselov, 2007; Novoselov et al., 2004; Rao et al., 2009) are among widely explored non-traditional semiconducting materials to be transducers. (Fu and Li, 2010; Novoselov et al.,

2004). Their exceptional properties correspondingly enable operation over wider temperature and dynamic ranges (Power et al., 2017). These carbon allotropes are biocompatible and possess a wide potential window accordingly permitting label-free detection of DNA hybridisation detection that is highly selective and specific (Fu and Li, 2010; Du et al., 2012).

2.3.2.2.1. Nanodiamonds/diamond-like carbon. Succeeding silicon and/or metallic nanoparticles, diamond has equally attracted attention as a promising alternative semiconductor material in DNA sensors. In comparison to materials like silicon and germanium, diamond has far more superior physical properties such band gap, carrier mobility, resistivity, thermal conductivity and thermal expansion (Vermeeren et al., 2009). Diamond has since became renowned to firmly bind DNA and its label-free detection (Song et al., 2006; Wenmackers et al., 2003; Yang et al., 2004, 2009a). Moreover, diamond is chemically inert, leading to stable biointerfaces in aqueous electrolytes (Vermeeren et al., 2009). Consequentially, multiple innovative nanodiamond-based DNA sensors have been developed. For example, Vermeeren et al. (2007) developed a label-free diamond-based DNA sensor that could distinguish between complementary and 1-base mismatched DNA targets during real-time hybridisation based on impedance. Through a nanocrystalline diamond, Cornelis et al. (2014) achieved real-time and label-free DNA hybridisation quantification based on heat transfer resistance. In another study, a nanocrystalline diamond field-effect sensor was demonstrated to exhibit exceptional sensitivity to DNA hybridisation when compared to a microcrystalline diamond field-effect sensor (Izak et al., 2015).

Although, multiple electrochemical nanodiamond-based DNA sensors have been demonstrated in scientific literature, the commercial application of these electronic devices has yet to be exhaustively explored. The lack of widespread commercial applications of nanodiamond and/or diamond-like carbon sensors is due to the costly large-scale nanodiamond production and refinement methods (Power et al., 2017). Novel cost-effective procedures used to fabricate diamond nanowires for DNA sensing applications have been reviewed by Yang et al. (2009b). It is also noteworthy to highlight that, not a lot of research advancement and/or developments of DNA sensors have been demonstrated using nanodiamond and/or diamond-like carbon materials in almost a decade. This is reflection of the shift in research interest/attention to 'modern' nanomaterials such as graphene and carbon nanotubes discussed in the next sub-sections. Refer to Wenmackers et al. (2009) for a detailed appraisal of advances made in the last decade in diamond-based DNA sensors from a surface functionalisation and signal transduction strategy point of view.

2.3.2.2.2. Carbon nanotubes. Since their 're-discovery' in 1991 (Iijima, 1991), carbon nanotubes (CNTs) have become one of the most studied nanoparticles in various fields due to their unique optical, thermal, mechanical and electrical properties (Bernholc et al., 2002). CNT substrates are considered attractive alternatives for silicon-based microelectronic devices mainly due to their superior electrical properties (Mustonen et al., 2015). Comparable to traditional materials, when used as electrode interfaces in electrochemical reactions, CNTs have been demonstrated in scientific literature to:

- Possess good chemical and conductivity stability (Power et al., 2017);
- Exhibit extraordinary electron transfer capabilities (Yang et al., 2015); and
- Possess supplementary edge sites and easier surface functionalisation (Ates, 2013).

Due to their ability to behave as either semi- or metallic-conductors, CNTs can be utilised in integrated circuits as transistors and/or components of transistors (Cao et al., 2015; Chen et al., 2016). The employment of CNTs as remarkable sensitive sensors is permitted by their high sensitivity to surface conductivity changes in the presence of adsorbates (Power et al., 2017). Due their inherent electrical conductivity, CNTs substrates offer significant improvements in the performance of DNA sensing devices such as (1) DNA signal amplification (Li et al., 2012; Primo et al., 2014); and (2) improved sensitivity to DNA (Ozkan-Ariksoysal et al., 2017). Consequently, CNTs are highly exploited as DNA biocompatible materials in a plethora of electrochemical sensors. (Power et al., 2017). Fabrication methods of such CNT-DNA hybrid systems and their applications in DNA sensing are described extensively by Rasheed and Sandhyarani (2017) and Cho et al. (2017).

CNTs are hollow cylinders of graphene sheets that exist in different forms/types with varying thickness, size, morphology, and metallic/semiconducting properties (Gibson et al., 2007). The different types of CNTs range from single-walled (Odom et al., 2002), double-walled (Pfeiffer et al., 2008), multi-walled (Kukovecz et al., 2013) to stacked-cup CNTs (also known as carbon nanofibers) (Kim et al., 2005). Compared to metallic and diamond nanoparticles, multi-walled CNTs exhibit greater electrical conductivities thus making their incorporation into electrical DNA transduction schemes favourable (Abu-Salah et al., 2010; Kukovecz et al., 2013). Numerous technologies that take advantage of the nanostructure of multi-walled CNTs for ultra-sensitive label-free detection of DNA have been developed (Clendenin et al., 2007; Li and Lee, 2017; Star et al., 2006; Tang et al., 2006; Tam et al., 2009). Contrasting multi-walled CNTs, which behave strictly as semiconductors, depending on the diameter and chirality, single-walled CNTs can act as either semi- or metallic-conductors thus complicating their utilisation in the construction of stable sensing systems (Jeng et al., 2006; Odom et al., 2002; Liu et al., 2013; Yang et al., 2007).

For electrochemical sensing applications, CNTs are usually activated by removing end caps through acid treatment thereby creating oxygen functional groups and defect sites that aid in adsorption and electron transfer (Gao et al., 2012; Zhang et al., 2011). In doing so, other materials such as carbon nanotube fibers are additionally produced from CNTs (Vamvakaki et al., 2007; Wang and Lin, 2008). Although cylindrical and hollow as single-, double-, and multi-walled CNTs; the hollow cylinders of carbon nanofibers are made of graphene sheets that are tilted from the fiber axis in stacked plate, cup, or cone arrangements (Kim et al., 2005). Additionally, it is cheaper to produce these stacked-cup CNTs (carbon nanofibers) as they require simpler functionalisation processing techniques compared to single-, double-, and multi-walled CNTs (Kim et al., 2005; Vamvakaki et al., 2007; Wang and Lin, 2008). This opens new prospects for the development of novel types of nanotube-based DNA sensing and sequencing technologies. For instance, sensors that specifically and selectively bind complementary DNA have be created by simply attaching oligonucleotide probes around the ends of vertically aligned carbon nanofibers (Lee et al., 2004; Koehne et al., 2009). Recently, using a carbon nanofiber-based sensor simultaneous, selective, and specific detection of purine bases in real fish sperm DNA samples was achieved (Lu et al., 2015). However, it is worth highlighting that carbon nanofiber-based biosensors that are reported in literature are scarcely for DNA detection. Carbon nanofiber-based biosensors are mostly reported for principal sensing of enzymes and antibodies (Sapountzi et al., 2017).

Overall, CNTs and carbon nanofibers reportedly supply faster response times due to their nano-porous nature (Ates, 2013). Tran et al. (2017) recently developed a CNT-based sensor for label-free detection of an influenza A virus that had a response time of less than 1 min. Furthermore, 97% of that sensor's output signal was recovered after 7 months storage. While significant advances such as the aforementioned can be accomplished in DNA sensing using CNTs on their own, incorporating CNTs with other nanoparticles such as metallic nanoparticles and polymers into composites has also seen increased interest (the utilisation of composite nanomaterials in DNA sensing is discussed in Section 2.3.2.4 of this review). All the same, despite CNTs/carbon nanofibers still having a wide scope for application in DNA sensing technologies; the field of carbon nanomaterial-based DNA sensors has

significantly expanded and recent trends have witnessed a rapid shift towards the use of graphene and graphene related materials (Yang et al., 2015). Thus, in this present-day review it is only befitting that a coherent but yet condensed and/or concise viewpoint of the status quo in carbon-based nanomaterial for DNA sensing is provided using graphene as not only the current representative material for carbon-based nanomaterials but as the basic building block of most carbon-based nanomaterials. Accordingly, the features of graphene and graphene-related materials in DNA sensing, insights on DNA-graphene interactions; and nanotoxicity concerns of the use of graphene and graphene-related materials in biological/biomedical applications are the main focus of this review and thus discussed in the next subsection.

2.3.2.2.3. Graphene. Due to the distinctly unique thermal conductivity (4.8×10^3 to 5.3×10^3 W/mK) superlative structural strength (40 N/m), and incredible electronic flexibility of graphene (Balandin et al., 2008; Geim, 2009; Neto et al., 2009; Novoselov et al., 2004; Geim and Novoselov, 2007) as opposed to all the other carbon allotropes; graphene and graphene related materials are currently explored and used worldwide in biosensor and electronic devices as suitable biocompatible DNA immobilisation platform. Since its first discovery in 2004, this simple sp^2 hybridized planar monocrystalline carbon structure has earned its discoverers, Novoselov and Geim, a nobel prize. Graphene has been shown to be the first of any atomic thin material to exhibit thermodynamic stability under ambient conditions whilst maintaining its continuous honeycomb network nature (Novoselov et al., 2004). Adding to and corroborating Novoselov et al. (2004) initial findings, this flexible two dimensional material has been reported to exhibit novel optical, mechanical, ballistic electron transport, thermal conductivity, and electronic properties (Allen et al., 2009; Balandin et al., 2008; Neto et al., 2009; Geim and Novoselov, 2007; Lee et al., 2008; Rao et al., 2009; Stampfer et al., 2008). As a result, graphene is by far the most versatile transducer as it can be used in electrical and electrochemical (Chen et al., 2010; Dong et al., 2010; Mohanty and Berry, 2008; Zhou et al., 2009), optical (Dong et al., 2010; He *at al.*, 2010; Jang et al., 2010; Lu et al., 2009; Xie et al., 2009) and other transduction schemes for DNA detection in variety of medical, environmental and industrial diagnostic applications (Feng et al., 2011; Heller et al., 2006; Lu et al., 2010).

The first and perhaps the most crucial step in achieving the necessary result in analytical applications involving detecting DNA hybridisation using graphene through various novel schemes, is the synthesis of high quality graphene with no residual defects (Du et al., 2012). To date the fastest and most reliable method used to effectively produce graphene of the highest quality is the micro-mechanical exfoliation method first invented by Novoselov et al. (2004). Although most successful graphene synthesis method, mechanically exfoliating highly oriented pyrolytic graphite (HOPG) using an adhesive tape is difficult to control and not scalable. Therefore, other methods of graphene synthesis have been developed. These methods include chemical synthesis of graphene, epitaxial growth of graphene on silicon carbide (SiC) (Berger et al., 2006; Emtsev et al., 2009) and chemical vapor deposition (CVD) of hydrocarbons on metal substrates (Li et al., 2009; Reina et al., 2008; Sutter et al., 2008). These methods are yet to be made feasible for large-scale production of high quality graphene since they typically produce highly modified, low quality graphene (Zhang et al., 2014).

In fact, majority of graphene based sensors developed to date do not use graphene at its purest form. Graphene related materials such as graphene nanocomposites, reduced graphene oxide (RGO), graphene oxide (GO) and few-layered graphene oxide sheets are increasingly explored and subsequently reported as a sensitive and selective suitable platforms for graphene based transduction of DNA hybridisation. Although its detailed structure is not elucidated in detail in literature, GO is hydrophilic graphene layered flakes that consists of epoxy (C-O-C), carboxyl (-COOH) and hydroxyl (-OH) oxygenated functional groups randomly located on the edges and basal graphene surface (Dikin et al., 2007). This chemically functionalisation of graphene makes the resulting GO more biocompatible and easily modified for application in any desired application particularly biomedical/biological related applications. Due to the polarity and ionizability of the oxygen-containing functional groups on GO, GO is hydrophilic in nature thus allowing for easy GO dispersion in water and wider range polar organic solvents (Dikin et al., 2007; Compton and Nguyen, 2010; Eda et al., 2008).

Although these devices are low cost, rapid highly sensitive and selective DNA sensors which demonstrated low detection limits, the majority of these devices use GO and not graphene. Understandably so GO has improved biocompatibility compared to pristine graphene. Nonetheless GO presents' toxicity problems in biological/biomedical applications. One study reported that of all graphene material, GO was the most toxic when dispersed in the lungs of mice. GO was found to be toxic unlike pristine graphene (Duch et al., 2011). Ahmed and Rodriques (2013) recently corroborated this in activated sludge where GO was found to have an acute toxic effect that lead to oxidative stress and entrapment of bacterial cells. This reduced the microbial community metabolic activity, biogeochemical cycles of carbon, nitrogen, phosphorous) and ultimately deteriorating the waste water treatment process. It is worth noting that in this study the toxic effect of GO was observed at GO concentration range of 50–300 mg/L (Ahmed and Rodrigues, 2013). The hydrophobic nature of pristine graphene makes it insoluble in aqueous solutions and as a result prone to large aggregation. On the other hand, GO is soluble in aqueous solutions. Recently, the stability and mobility of GO nanoparticles in soil, groundwater and surface water was studied. It was observed that GO nanoparticles were less stable and highly mobile particularly in surface waters (Lanphere et al., 2014). Although shown to have diminutive impact in ground water, due to these toxicological effects and mobility of GO nanoparticles the use of GO raises safety concerns. Bioaccumulation of GO could disrupt the ecosystem and result in human health consequences for individuals exposed to GO. In biosensor development and commercialisation, the safety of the sensing device is very important. This is particularly important in DNA hybridisation detection as it has tremendous potential opportunities to be marketed and commercialised for use in various biological/biomedical technologies.

The development of graphene-based DNA biosensors only started a few years after the 2004 discovery of graphene (Novoselov et al., 2004; Geim and Novoselov, 2007). As depicted in bibliometric data in Fig. 6, the first publications that made reference to the use of graphene in DNA biosensors were published in 2008. Since then graphene-based DNA biosensors have been explored every year. Detection of DNA hybridisation using graphene based sensors depends primarily on successful immobilisation of the single-stranded (ss) DNA probe as the bioreceptor onto the graphene transducer to form controllable ssDNA probe-graphene nanocomposites. The immobilisation of DNA on the support transducer material is crucial in the development of DNA-based microarray and biosensing technologies as it can impact on the quality of detection of DNA. Immobilisation of the probe should in all possible efforts maintain the inherent complementary affinity of the probe for its specific target DNA but yet be predictable and precise (Malmqvist, 1993; Lucarelli et al., 2008; Tang et al., 2011).

Other innovative approaches of DNA immobilisation on the graphene surface such as covalent linkage and affinity binding have been explored. However, adsorption namely spontaneous self-assembly is the simplest immobilisation approach of label-free ssDNA probes most successful and specific to graphene and its derivatives (Oliveira Brett and Chiorcea, 2003). See Lucarelli et al. (2008) for a detailed review of immobilisation approaches most appropriate and specific for other electrodic materials. Onto the solid/crystalline surface of graphene, ssDNA probes are reversibly and non-specifically adsorbed. This adsorption is characterized by non-covalent spontaneous self-assembly (Lucarelli et al., 2008; Tang et al., 2011; Malmqvist, 1993). Adsorption of the ssDNA probe oligonucleotide in the buffer (in the solution it is

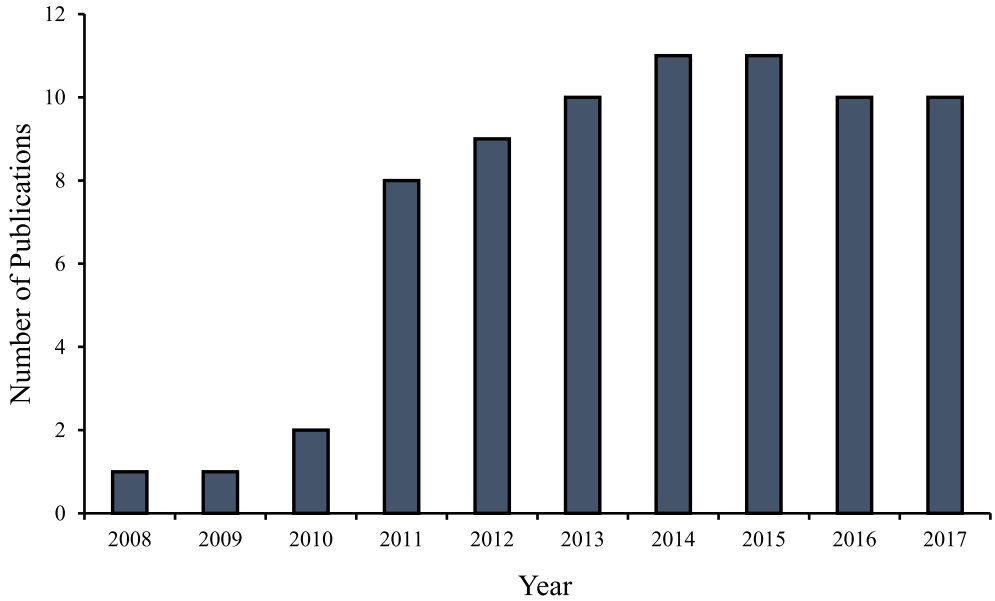

Fig. 6. Bibliometric survey analysis, for the year 1985–2017, using data provided in Scopus SciVerse of publications related to graphene-based DNA sensors.

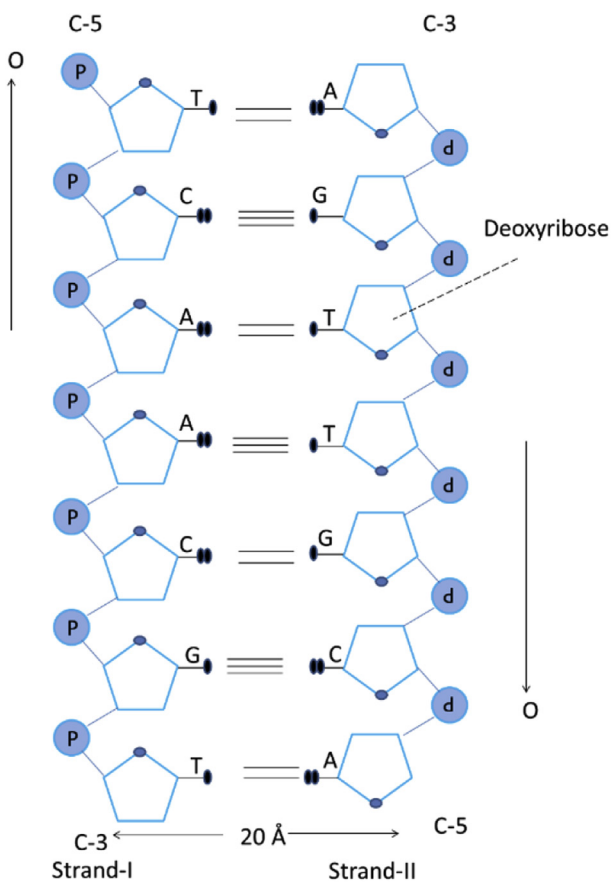

Fig. 7. Schematic illustration of the basic structural units of DNA. A = Adenine, C= Cytosine, G = Guanine, T = Thymine, P= Phosphate group (Adapted from Wolcott, 1992).

prepared in sterile deionised water or buffer solution, namely trisaminomethane-ethylenediaminetetraacetic acid (Tris-EDTA) buffer) results in the formation of self-assembled monolayer/film of the ssDNA probe (adsorbate) on the surface of the graphene (adsorbent). As depicted in Fig. 7, the atomic structure of the ssDNA probe is basically a phosphate-deoxyribose sugar backbone held together by 3′-5′ phosphodiester bonds that consist of a phosphate groups (PO_3^{-4}) at the 5′ end and the deoxyribose sugar ($C5H_{10}O_4$) at the 5′ end and 3′ end, respectively (Wolcott, 1992).

Due to the strong affinity of the phosphate group to the graphene substrate, to form the self-assembled monolayer of helical ssDNA probes on the graphene surface, chemisorption of the phosphate groups (PO_3^{-4}) on the 5' end of each of the DNA probes with the graphene carbon atoms occurs. (Gooding, 2002; Oliveira Brett and Chiorcea, 2003; Kerman et al., 2003; Lee et al., 2008; Tang et al., 2010). Theoretical simulations predict the ssDNA probe molecule to possibly be geometrically perpendicular to the graphene surface when phosphate groups are then anchored onto the surface (Aliofkhazraei et al., 2016; Zhou, 2015). On the graphene surface, the ssDNA probe molecule is not entirely enclosed and can subsequently bind to complementary DNA targets upon hybridisation. In fact upon hybridisation with its target ssDNA, the interactions between the ssDNA probe and graphene is weakened as the initial DNA adsorption onto the graphene surface is reversed. Similar to DNA adsorption, DNA desorption from the graphene is prompt and highly efficient. Following desorption, the ssDNA probe and its complementary target ssDNA hybridise and form a double-stranded (ds) DNA duplex (Gooding, 2002; Oliveira Brett and Chiorcea, 2003; Kerman et al., 2003; Lee et al., 2008; Tang et al., 2010; Du et al., 2012; Ngo et al., 2013).

Studies exploring the detailed mechanisms employed by ssDNA to bind to graphene are limited (Gowtham et al., 2007). As a result, aspects concerning binding mechanisms and; (2) quantification of the exact type and relative strength of DNA-graphene interactions that exist within ssDNA probe-graphene nanocomposites are not well understood (Oliveira Brett and Chiorcea, 2003; Tang et al., 2010). Nonetheless, it has been shown through DNA interactions with the graphene layer on the surface of highly ordered pyrolytic graphite, that ssDNA and graphene may be bound together by means of pi (π) base stacking, van der Waal interactions, hydrophobic interactions, electrostatic interactions, and hydrogen bonding while others have suggested that DNA interacts with graphene via weakly attractive dispersion forces induced by molecular polarisability (Oliveira Brett and Chiorcea, 2003; Gowtham et al., 2007; Lee et al., 2013).

Thermodynamic and kinetic studies of: (1) the structural DNA conformation changes that occur to the ssDNA probe and its nucleobases when immobilised on graphene; and (2) behavioural changes that ssDNA probe-graphene nanocomposites undergo to exert the necessary response signal in various novel platforms revealed that spontaneous

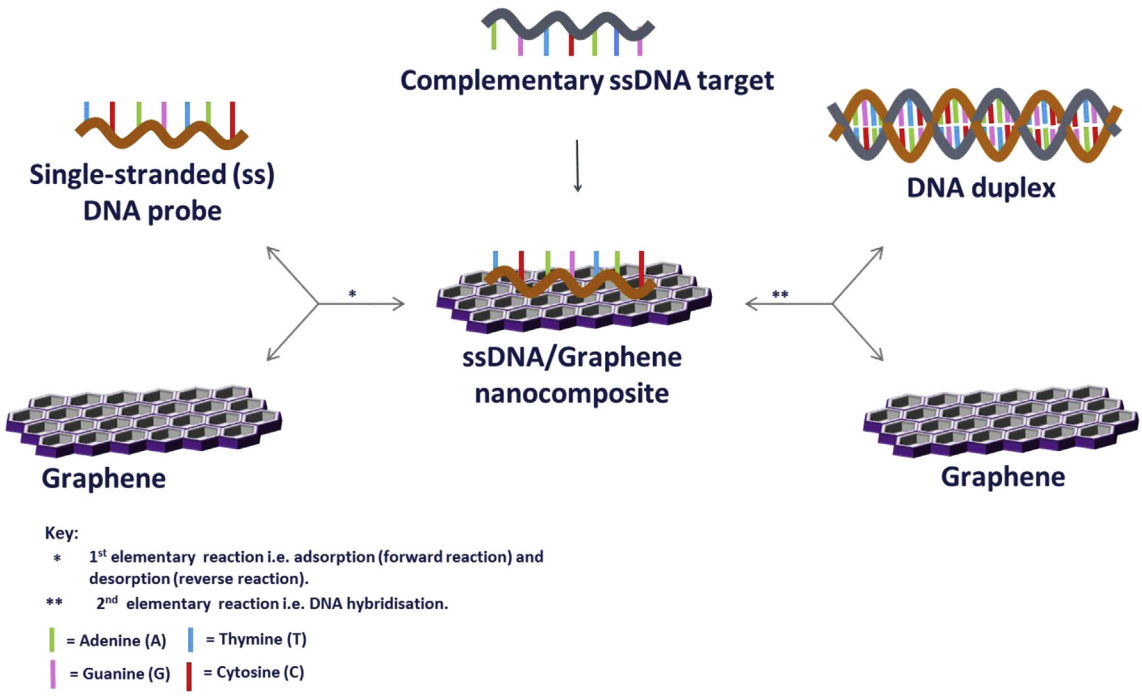

Fig. 8. Macroscopic illustration of DNA adsorption and desorption on graphene (Adapted from Du et al., 2012).

self-assembly immobilisation of ssDNA probes involves physisorption of the individual DNA nucleobases onto the graphene surface (Akca et al., 2011; Das et al., 2008; Gowtham et al., 2007; Varghese et al., 2009). In this case, theoretical simulations predict the ssDNA probe molecule to lay flat parallel to the graphene surface as depicted in Fig. 8 (Aliofkhazraei et al., 2016; Zhou, 2015).

Previous theoretical and experimental studies have been published separately approximating and calculating nucleobase interaction with graphene and its derivatives including carbon nanotubes by assuming π base stacking, van der Waal interactions, hydrophobic interactions, and hydrogen bonding (Das et al., 2008; Gowtham et al., 2007; Nandy et al., 2012; Varghese et al., 2009). However, electrostatic interactions have not been considered interactions which determine DNA nucleobase interactions with graphene (Akca et al., 2011; Nandy et al., 2012).

Some of these theoretical models using first-principles density functional theory (DFT), plane wave pseudopotential local density approximation and ab-initio quantum chemical Hartree–Fock method coupled to the second–order Møller–Plesset perturbation theory frameworks and calculations have shown that during this physiosorption, the nucleobases guanine (G), adenine (A), thymine (T), cytosine (C), and uracil (u) [uracil in RNA] bind to graphene with similar equilibrium configurations. However, their binding energies scale in the following hierarchical order: G > ÃT ~ C > U. (Gowtham et al., 2007; Mukhopadhyay et al., 2010; Varghese et al., 2009). However, theories based on van der Waal (vdW) interactions report the following hierarchy of nucleobase binding with graphene; (G > ÃT > C). Overall vdW theoretical calculations supported by experimental studies such as isothermal titration (micro) calorimetry conclude that the overall trend of nucleobase-graphene interaction energy is: G > A > T > / < C when solvation effects are accounted for or taken into consideration (Das et al., 2008; Gowtham et al., 2007; Varghese et al., 2009). Theoretical and experimental models based on vdW interaction being the dominating interactions have efficiently explained with not only the nucleobase-graphene/carbon nanotube binding energies but also managed to account for some geometrical observations made especially in carbon nanotubes.

However, findings of a most recent study show that during immobilisation the DNA molecule adopts two distinct conformations that appear to be in total disagreement with the known interactions models predicted to be involved in DNA-graphene interactions (Akca et al., 2011). Using projective measurements of nucleobase-nucleobase interactions, Akca et al. (2011) found that during immobilisation onto a graphene surface, within the DNA molecule the poly-A and C form spherical particles while the poly-T and G form elongated networks. These findings, suggest the existence of competitive stacking between DNA nucleobases-nucleobase and nucleobase-graphene. Furthermore, Akca et al. (2011) findings show no distinguishable involvement of hydrophobic interaction and do not support the previously predicted G > A > T > / < C hierarchy. Instead their findings lead them to suggest π stacking model that the purines, A and G bind to graphene with similar energies and pyrimidines, C and T also with similar binding energy interact with the graphene surface, (ÃC, T ~ G). In their structural and energetics studies via atomic molecular dynamics simulations, Manna and Pati (2013) collaborated Akca et al. (2011) findings. Manna and Pati (2013), suggest π–π stacking nucleobase–-nucleobase intra-molecular interactions being the ones responsible for maintaining the helical geometry of the DNA probe, while the intermolecular π–π stacking nucleobase–graphene interactions playing a fundamental role in the adsorption of the single stranded DNA probe onto the graphene surface.

DNA and graphene interfaces used in a wide range of sensor technologies have been published. Traditionally, optical DNA-graphitic biosensors explored fluorescence resonance energy transfer (FRET) to exploit the ability of graphitic carbon to quench fluorescence properties of fluorophores when adsorbed on its surface and subsequent restoration of the fluorescence upon hybridisation with a complementary target (Kagan and McCreery, 1994). DNA-graphene FRET biosensors have been used successfully to selectively detect both labelled (Jung et al., 2013; Liu et al., 2010) and non-labelled (He et al., 2010; Lu et al., 2009; Lu et al., 2010) complementary DNA strands. The use of fluorophores has been shown to enhance the devices sensitivity. However, this method of DNA detection on graphitic transducer surfaces such as graphene might affect the DNA probe's bioaffinity, increases complexity and cost of analysis (Lee, 2008; Özkumur et al., 2010). Therefore, despite graphene's compatibility with optical transduction modes of DNA hybridisation detection, direct modes of detection such as label-free

electronic/electrochemical transduction of DNA hybridisation are currently the most studied (Wu et al., 2010).

Due the unique electron transfer properties of graphene and graphene related materials (Chen et al., 2010), DNA-graphene hybrids are investigated in electrochemical/electrical sensors. In addition to label-free DNA hybridisation detection, electrical sensors offers rapid DNA hybridisation detection with single-base mismatch specificity and sensitivity as low as 0.1 pM of DNA (Bonanni and Del Valle, 2010; Dong et al., 2010; Lin et al., 2011; Wu et al., 2010). The most common and promising type of label-free electrochemical or electrical sensors that are heavily explored are primarily, metal oxide semiconductor field effect transistor (MOSFET) and field-effect transistor (FET) devices (Green and Norton, 2015). Graphene is an enticing construction materials for FET based devices. This is attributed to mainly to its ambipolar nature and biocompatibility to DNA hence using graphene in FET sensors requires no prior sensor or DNA functionalisation (Geim and Novoselov, 2007; Green and Norton, 2015).

In recent FET based devices, the output transduction observed is due to the electrical properties of label-free DNA oligonucleotide (Millan and Mikkelsen, 1993; Bonanni and Del Valle, 2010). In such devices the actual label-free electrochemical or electrical detection of DNA hybridisation is achieved by monitoring the conductivity changes in graphene, where fluctuations in drain-source current-gate voltages of the graphene are measured (Torkel, 1959). From these current-gate voltage measurements, information on the carrier mobility and their corresponding carrier densities is extracted. The change in the current refers to characteristic differential responses of the DNA-graphene sensors' ability to chemically recognise and discriminate diverse and distinct molecular analytes in a sequence-dependent manner (Bo et al., 2011; Dong et al., 2010; Du et al., 2012; Feng et al., 2011; Lu et al., 2010). Therefore, adsorption of ssDNA probe onto the graphene surface and desorption upon hybridising with complementary ssDNA target does not only result in the surface potential modulation but it is also the sensing scheme of FET based sensing technologies (Lin et al., 2011; Du et al., 2012).

Despite attempts to understand the theoretical principles involved in adsorption and desorption of DNA on graphene, little is known about the nature of DNA structure and conformation on graphene (Akca et al., 2011; Gowtham et al., 2007; Lin et al., 2013; Mukhopadhyay et al., 2010; Varghese et al., 2009). In FETs the introduction of DNA presents challenges that further complicate the sensing scheme. Buffer effects, doping, chemical/electrostatic gating, and induced dipoles could induce changes in graphene's electronic and structural properties thus affecting DNA detection and sensitivity (Kergoat et al., 2010; Mohanty and Berry, 2008). Furthermore, graphene has been reported to disrupt the structure of folded DNA Husale et al., (2010); Liu et al. (2011); Wu et al. (2014)]. Therefore, despite proof of concept demonstration of application of FET that are produced at low cost and possess impressive DNA detection limits, the exact cause of the commonly studied modulation in gate voltage observed in DNA graphene-based FET devices is unknown (Bonanni and Del Valle, 2010; Lin et al., 2013).

Consequently, in literature there are discrepancies in the reported observed shifts in gate voltage and perceived cause of the shifts (Chen et al., 2009; Dong et al., 2010; Lin et al., 2013). There are literature reports of DNA graphene-based FET devices that show large gate voltage shifts in both positive and negative potential directions. Recently, a group reported a significant positive shift in gate voltage observed upon DNA immobilisation on their FET based chemical vapour sensor. And they attributed this shift in the positive direction to a counteractive effect to overcome the induced negative field due to the negatively charged nature of DNA's phosphate backbone (Kybert et al., 2014). Similarly, other previously published studies have demonstrated a negative potential shift of the gate voltage on DNA deposition on graphene (Chen et al., 2009a; Wang et al., 2013). Dong et al. (2010). However, unlike previous studies that claimed the negative gate voltage bias to be due to electrostatic gating (Artyukhin et al., 2006), buffer effects (Chen et al., 2009b) and ionic impurities masking (Chen et al., 2009b; Wang et al., 2013), n-doping effect is an argument that was previously ruled out (Lerner et al., 2012). The n-doping effect caused by the π–π stacking of the electron-rich nucleobases was ruled out together with charge injection by Lerner et al. (2012) in a study performed on charged DNA strands of varied lengths tethered on graphitic surface in a FET sensor.

Negative voltage gate potentials have also been explained in literature to be due to mechanisms such as chemical doping by adsorbates (Lu et al., 2010b), n-doping (Yin et al., 2012) and p-doping (Mohanty and Berry, 2008). Lin et al. (2013), proposed recently that instead of using gate voltage to qualitatively monitor DNA hybridisation, using sheet resistance and carrier mobility could address the reported measurement inconsistencies. Lin et al. (2013), claimed that electrical mechanisms involved in DNA graphene interactions did not occur consecutively but instead all three, that is, masking charge impurities, graphene doping and electrostatic occurred simultaneously. Inconsistencies in reported literature measurements are mainly due to the lack of in-depth understanding of interactions involved between DNA and graphene. But is also equally important to note that differences in design and composition of the device and analysed samples has a role in the current confusion (Green and Norton, 2015).

2.3.2.3. Metal oxide nanoparticles. Metal oxide nanoparticles are equally known to offer a wide range of possible functional and biocompatible surfaces for biosensing applications (Comini and Sberveglieri, 2010). Nanostructured metal oxides expand the novelty horizon for a variety of DNA diagnostics applications (Solanki et al., 2011). Titanium oxide, tin oxide, and iron oxide nanoparticles prepared on pencil graphite electrodes are amongst the first metal oxides to be explored as functional surfaces for DNA detection almost a decade ago (Mathur et al., 2009). In that study, the metal oxides not only formed important cost-effective components of the disposal electrochemical DNA sensor but were found to enhance the detection limits down to nano-molar DNA concentrations ranges (Mathur et al., 2009). Since then a wide range of nano-structured metal oxides have aroused interest as DNA biocompatible materials (Solanki et al., 2011). Zinc oxide is amongst the widely exploited metal oxide nanoparticles for sequence specific and selective DNA hybridisation detection (Mohammed et al., 2017; Yumak et al., 2011; Wang et al., 2015). Other metal oxides such vanadium oxide and cerium oxide nanoparticles which are widely studied in other fields are also slowly finding employment in DNA hybridization detection systems. A single DNA base specific sensors based on vanadium pentoxide nanofibers was recently developed by Annalakshmi et al. (2018). The vanadium pentoxide nanofibers were not only found to selectively detect adenine with a sensitivity of about 8.5333 $\mu A\,\mu M^{-1}\,cm^{-2}$ but it was also found to have good recovery in real human urine samples. Detection of DNA in real samples has been difficult to achieve using other nanoparticles such as graphene oxide due to non-specific DNA displacement by protein that is prone to occur in these nanoparticles (Wu et al., 2011). Cobalt oxide nanoparticles have also been demonstrated by Liu et al. (2018) as resistant to non-specific protein displacement thus enabling detection of trace levels of DNA in real samples. Therefore, the use of metal oxide nanoparticles such as vanadium oxide and cobalt oxide opens up multiple avenues for the development of DNA sensors for use under a multitude of realistic conditions.

Recommencing, the ability of nanoceria (cerium oxide nanorod) to detect DNA of a food-borne infection-causing bacteria, *Salmonella*, was recently demonstrated by Nguyet et al. (2018). Nanoceria undergoes optical changes upon interaction biomolecules such as DNA. This optically active nature of nanoceria makes it an attractive nanomaterials for fabrication of portable label-free DNA sensors for food and related industries from a safety assessment point of view (Bülbül et al., 2015; Kumara et al., 2015). Unlike the adsorption to DNA to metallic

nanoparticles and carbon-based nanomaterials' known to be governed by inter-molecular π–π stacking nucleobase interactions; insights regarding interactions between metal oxides and DNA are not well known despite successful demonstrations of DNA detection capabilities of metal oxides nanoparticles (Liu and Liu, 2015).

2.3.2.4. Nanocomposites. In recent years, there have been improvements in DNA sensing devices made possible due to the use of nanomaterials (Fernandes et al., 2014). Multi-functionality and synergism can be added to inert noble metal nanoparticle-based sensor systems by systematically integrating/compounding of multiple nanomaterials of different functions and/or properties to form DNA compatible nanocomposite materials (Mandal et al., 2018). As a result, the use of nanocomposite materials is rapidly eclipsing that of monometallic nanoparticles in DNA sensing. Metallic nanoparticles are commonly integrated with carbonaceous nanomaterials for selective detection on DNA (Zhang et al., 2010; Zhu et al., 2005). Such an integration of nanoparticles was recently demonstrated by Yola et al. (2014) using a Fe-Au nanoparticles decorated 2-aminoethanethiol functionalized graphene oxide sensing platform. Through that novel sensing platform, a one-to three-base selective detection of mismatched DNA was electrochemically observed with a detection limit low down to 2.0×10^{-15} M. A similar detection limit (10×10^{-15} M) in a similar concentration range was obtained by obtained by Gao et al. (2008) using a 3′ thiol labelled oligonucleotide probe for selective electrochemical detection of three-base mismatch during DNA hybridisation using silver-nanoparticle loaded multi-walked CNTs.

When incorporated with other nanoparticles such as metallic nanoparticles and polymers into composites, CNTs are known to have enhanced electron transfer abilities which lead to enhanced performances in DNA sensors (Liu et al., 2009). This enhanced behaviour was demonstrated by Zhang et al. (2008) on a multi-walled CNTs/ZnO/chitosan nanocomposites which was found to effectively detect DNA hybridisation with greater sensitivity compared to pure CNTs. Jiang and Lee (2018) used an electrochemical impedance based CNT/polymer (polydimethylsiloxane) sensor and observed that not only could it detect single base-pair mismatches but it was able to reduce the detection limit down to 25×10^{-15} M and response times to less 30 min from 1 h. In another study, Zhang et al. (2009) designed an electrochemical sensor based on silver nanoparticles/poly (*trans*-3-(3-pyridyl) acrylic acid)/multiwalled carbon nanotubes with carboxyl groups modified glassy carbon electrode for DNA hybridisation detection. Although this sensor had a detection limit of 3.2×10^{-12} M, showed excellent stability and reproducibility during complementary DNA hybridisation; it was unable to exhibit obvious detection signals for mismatched and non-complementary DNA strands despite the use of 5′ thiol labelled oligonucleotide probes. Detection limits down to a 1.0×10^{-12} M range have also been achieved during DNA hybridisation detection using gold/multi-walled CNT nanocomposites with methylene blue labelled DNA probes (Gu et al., 2007). The difference observed in detection by the various studies that integrated CNTs and metallic nanoparticles discussed above, reveal an important role and potential influence that different types of DNA labels can have on signal transduction. Earlier advances involving various kinds of CNT-based hybrid nanomaterials for DNA detection have been comprehensively reviewed by Yogeswaran et al. (2008).

The use of metallic nanoparticles in a form of dichalcogenides equally emerged. Dichalcogenides nanomaterial that are sought-after in recent times as attractive DNA biocompatible support are molybdenum disulfide nanosheets (Gan et al., 2017). The two-dimensional nature of molybdenum disulfide nanosheets allows for the fabrication of unconventional electrochemical, electronic, and optical DNA biosensors (Park et al., 2016; Singhal et al., 2018). Unlike three-dimensional semiconductors such as silicon, two-dimensional nanomaterials such as molybdenum disulfide are effectively modulated by electrostatic effects of charged target molecules such as DNA (Zhang et al., 2015; Zhu et al., 2013). Molybdenum disulfide nanosheets are also increasingly attracting commercial interest over one-dimensional nanoparticles such as CNTs (Kukkar et al., 2018). One-dimensional nanomaterials, such as CNTs are not feasible for large-scale fabrication of electronic devices such as field-effect transistors (Park et al., 2016). Due to the outpouring scientific and commercial interest that molybdenum disulfide nanosheets has attracted, there already exists numerous highly comprehensive reviews in open literature that have explored and compiled recent data/advances made using molybdenum sulfide nanosheets in DNA sensing (Barua et al., 2018; Kukkar et al., 2018; Hu et al., 2017; Wang et al., 2017; Yan et al., 2017). Therefore, specific aspects and advances involving the fabrication of molybdenum disulfide/DNA/aptamer biosensors and their application will not be replicated in this article. Overall, the various possible combinations of different nanoparticles that can be explored to form nanocomposites for specific and selective DNA detection are limitless. Monometallic nanoparticles can be integrated with other monometallic nanoparticles to form bimetallic, trimetallic, etc., materials (Mandal et al., 2018). Metal oxides can be combined with carbon-based nanoparticles (Solanki et al., 2011). Metallic nanoparticles combined with synthetic polymers such as latex as in the study performed by Pinijsuwan et al. (2010).

2.3.3. Transduction methods in DNA sensing

The most common and intensively explored mode of DNA hybridisation detection in biosensors is optical. It is highly selective and sensitive with detection limits as low as 10^7 biomolecules/cm^2 (Drummond et al., 2003). Screening techniques that are based on measuring an output signal through photometric processes are employed in optical transduction. As a result, optical transduction of DNA hybridisation requires multifaceted and expensive instruments (Drummond et al., 2003). The most common techniques which inherently require sophisticated instrumentation used to optically detect DNA hybridisation are fluorescence resonance energy transfer (FRET), reflectance spectroscopy, and Raman scattering and Fourier transform infrared (FTIR) spectroscopy (Velusamy et al., 2010). These techniques are incompatible with the portable idealism that biosensors are required to possess (Gooding, 2002).

Therefore, other transduction methods such as mass-sensitive and electrochemical signal transduction have been explored. In mass-sensitive signal transduction, changes in physical mass or surface properties in the bio-recognition layer are monitored during the bio-recognition event (Drummond et al., 2003). Mass-sensitive transductions using gold as a transducer support material have been reported to enable for a rapid label-free detection of DNA hybridisation in real-time (Karamollaoğlu et al., 2009; Passamano and Pighini, 2006). However, similar to optical transduction schemes, mass-sensitive signal transduction schemes involve the use multifaceted and expensive instruments (Drummond et al., 2003). As a result they are not commonly used as depicted by the low number of publications relative to other transduction methods (Fig. 9).

On the other hand, biosensors that are based on electrochemical transduction of DNA hybridisation are cheap, easy to operate and maintain as they do not require the use of expensive and complex systems (Drummond et al., 2003; Gooding, 2002; Hahn et al., 2005; Hvastkovs and Buttry, 2010; Kerman et al., 2003). In these biosensors, transduction of the bio-recognition event simply involves a direct transmission of electronic signal by the transducer. The type transducer that are typically used for direct transmission are semiconductors (Hahn et al., 2005; Hvastkovs and Buttry, 2010; Kerman et al., 2003). In electrochemical transduction of DNA hybridisation can be achieved through two novel approaches, redox active label assisted electrochemical transduction and label-free electrochemical transduction (Gooding, 2002; Hvastkovs and Buttry, 2010).

The discovery of redox-active labels laid the groundwork for the development of innovative DNA hybridisation biosensors. In label-assisted electrochemical transduction, the ssDNA probes that forms the

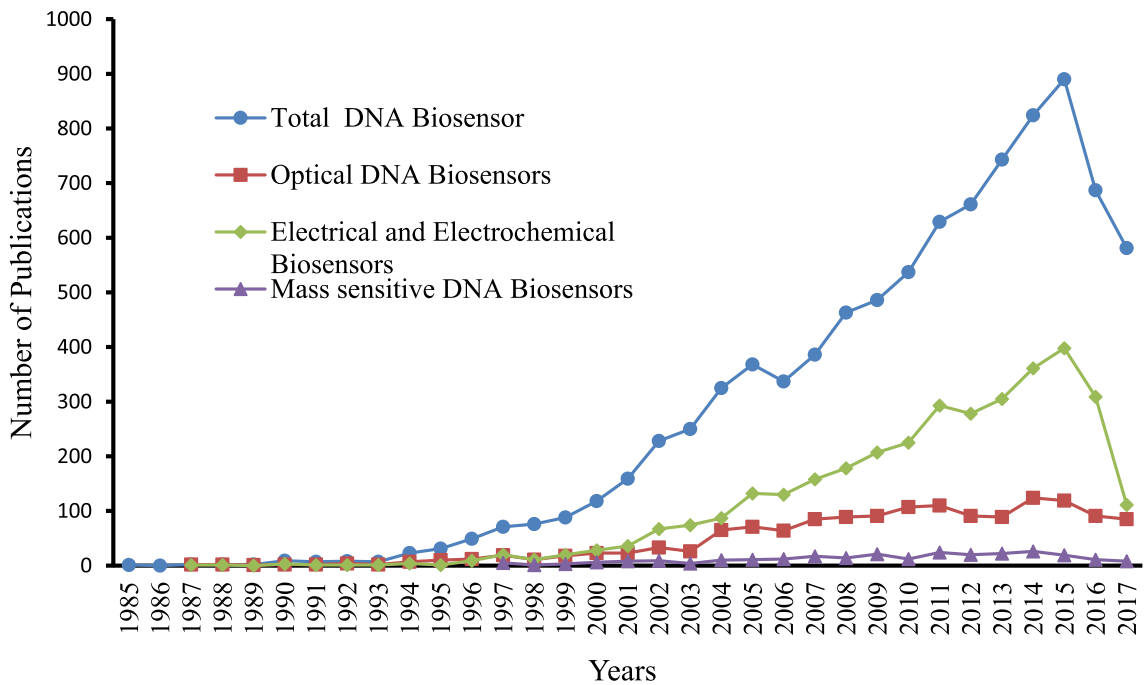

Fig. 9. Bibliometric survey analysis, for the year 1985–2017, using data provided in Scopus of publications related to different types of transduction methods in DNA biosensors.

bio-recognition layer are chemically modified by covalently attaching redox active labels on their nucleotide bases (Gooding, 2002; Kerman et al., 2003). These labels can be incorporated during the synthesis of the oligonucleotides, or later added through enzymatic or chemical reactions. Redox active labels that are commonly used range from organometallics to nanoparticles. (Kerman et al., 2003; Labuda et al., 2010; Zhu et al., 2006). These redox active labels enable transduction by gauging the interactions between the DNA probes on the bio-recognition layer and their targets during DNA hybridisation (Gooding, 2002; Kerman et al., 2003). Transmission of electrochemical signal is distinctly conveyed by these labels both before and after hybridisation through selective changes in their oxidation-reduction potentials (Velusamy et al., 2010). Generally, a greater electrochemical signal intensity is reported for the redox label modified DNA probe before its interaction with a complementary target (Gooding, 2002; Kerman et al., 2003). The incorporation of redox active labels on the DNA probes, increases their specificity. Furthermore, by incorporating diverse labels on a number probes with diverse nucleotide base sequences, multiple analysis of targets can enabled (Kerman et al., 2003; Labuda et al., 2010; Zhu et al., 2006).

As result, commercialised technologies that are based on this type of redox-active transduction such as Sensor™ and Genelyzer™, have been established and standardised. However, the covalent incorporation of redox labels in these technologies adds some complexity to the transduction scheme. Therefore making them not conform to the idealism that biosensors should be simple (Gooding, 2002; Kerman et al., 2003).

Therefore, label-free electrochemical transduction schemes are increasingly studied. Label-free electrochemical transduction is achieved through the direct and indirect use of unmodified DNA (Du et al., 2012). According to IUPAC standards, a probe is considered unmodified when it has no labels or when the labels are not covalently bound to the probe (Drummond et al., 2003; Labuda et al., 2010). The elimination of covalent incorporation of labels/indicators, simplifies the biosensor. In these label-free electrochemical biosensors, monitoring of DNA hybridisation is made possible through immobilisation of label-free or unmodified probes on a transducer with excellent electrochemical/electronic properties (Velusamy et al., 2010; Du et al., 2012). Therefore, label-free electrochemical transduction schemes are based on direct and/or indirect monitoring of changes in intrinsic electrochemical properties of the transducer during DNA hybridisation (Velusamy et al., 2010).

Electroactive noncovalent redox label are used for an indirect electrochemical detection of DNA hybridisation. Electroactive noncovalent redox labels are different from covalent redox active labels. Transmission of an electrochemical signal is achieved through the intercalation or binding of the noncovalent redox label to the double-stranded DNA duplex formed by the probe and its complementary target, accordingly specifically differentiating double stranded DNA duplexes from single stranded DNA structures (Drummond et al., 2003; Labuda et al., 2010). By measuring the noncovalent redox label's negative charge density using impedance and voltammetry, this differential electrochemical signal is monitored. Phenothiazine dye, and electrostatic ions such as the cationic $[Ru(NH_3)_6]^{3+/2+}$ and anionic $[Fe(CN)_6]^{3-/4-}$ complexes, and methylene blue are examples groove binders commonly used as noncovalent redox active labels in indirect label-free electrochemical DNA hybridisation transduction methods (Drummond et al., 2003; Labuda et al., 2010).

Akin to covalent redox label transductions schemes, the non-covalent redox label bound double-stranded probe-target DNA duplex also exhibit an electrochemical signal of greater intensity. This was proven consistent with previously reported literature in a recent study carried out by Siddiquee et al. (2010). In that study, an electrochemical DNA hybridisation biosensor to selectively and specifically detect a trichoderma harzianum related gene immobilised on a gold electrode was created. To observe the voltammetric transduction of DNA hybridisation, as the electroactive label, methylene blue was electrostatically bound to the probe on the gold surface and its voltammetric response upon formation of the DNA duplex was measured. The electrostatic responses of methylene blue were observed to be higher for the DNA duplex (Siddiquee et al., 2010).

From literature it is therefore evident that detection of DNA hybridisation has been successfully achieved using gold substrates through optical, mass-based and electrochemical signal transduction monitoring and analysis systems (Lockett et al., 2008; Shimron et al., 2013). However, the transition of gold-based electrodes to direct electrochemical DNA hybridisation detection without using labels has been

not successful. This is due to gold-based electrodes not possessing adequate electro-oxidation properties at positive potentials to detect electrochemical responses of unlabelled DNA. Moreover, the irreversible nature of electrochemical redox reaction in nucleobases prevents the reusability of DNA probes (Hvastkovs and Buttry, 2010; Labuda et al., 2010). As a result, for electrochemical DNA hybridisation biosensors that allows for reusability and improved electrochemical DNA detection limits while maintaining specificity and simplicity, non-traditional semiconducting transducer nanomaterials such as carbonaceous materials that possess controllable electronic and physical properties are explored (Fu and Li, 2010; Novoselov et al., 2004).

Direct label-free systems depend on intrinsic properties of DNA and its constituents. Properties exploited by these direct mechanisms are:

(1) DNA structural changes due to either the hydrophobic or polyanionic nature of nucleic acids. When tensammetric transitions occur in the DNA probe and its target DNA as they go from two single-stranded DNA strands to a double-stranded DNA duplex on the transducer, variations in conductometric, amperometric, potentiometric, and/or impedimetric responses are monitored and used as the electrochemical signal (Labuda et al., 2010; Velusamy et al., 2010).
(2) The electrochemical activity of nucleic acids. To quantitatively and qualitatively display DNA hybridisation, electroactive nucleotide bases such as guanine and adenine are used. The ability of guanine and adenine to undergo redox reaction makes these nucleobases electrochemically active. The electrical current transportation properties of DNA are due to this electroactivity. Therefore, upon formation of the DNA duplex, the change in the electrical current of electroactive nucleotide bases can be examined and used as a quantitative measure of an electrochemical output response (Kerman et al., 2003; Labuda et al., 2010).

This type of signal monitoring and analysis is made possible by excellent electrical properties of carbonaceous materials. Among the different carbonaceous materials, the most popular biocompatible materials used in fundamental research and commercial development of DNA sensing technologies are graphene, carbon nanotubes and graphite.

3. Current limitations and challenges of DNA biosensing technologies

Different transduction mechanisms and schemes have led to considerable successful development of biosensors in the academic arena with commercial potential to address multifarious applications in many fields (Mascini et al., 2001; Bora et al., 2013). In medical diagnostics, sensors are used to bio-medically detect infectious agents for both purposes of diagnostic and screening of diseases (Bora et al., 2013; Liao et al., 2006; Lee et al., 2008; Wang et al., 2011). In other industries, electrochemical DNA hybridisation biosensors have been demonstrated to be useful and reusable devices for the environmentally analysis of pollutants (Domínguez-Renedo et al., 2007; Lucarelli et al., 2008; Wang et al., 1997) and testing for food authenticity in the food and beverage manufacturing industry (D'souza, 2001; Nugen and Baeumner, 2008; Spadavecchia et al., 2005; Velusamy et al., 2010; Bora et al., 2013). Potential of commercialisation of biosensors in various fields is tremendous. However, because of several technology challenges, commercialisation of biosensors has been slow (Bora et al., 2013).

DNA is relatively stable compared to proteins and its use in DNA hybridisation biosensors is considerably promising in providing cheap and rapid detection of specific fragments of DNA. Equally, DNA hybridisation biosensors and bioelectronics have limitations that need to be considered. One limitation is bridging the gap between experimental research and reality (Hahn et al., 2005). Many of the DNA hybridisation biosensors developed especially for application in food authentication are perfect for the clean-cut laboratory conditions (Nugen and Baeumner, 2008). Ideally, targets used in food authentication should preferably undergo very little if any alterations during processing of food products. However, in real-life environmental, biomedical and industrial fields, several factors that may affect the integrity and quantity of DNA thus limit the effectiveness and reliability of DNA hybridisation biosensors (Lüthy, 1999). These factors include:

Storage of sample - For example, ineffectual traceability and authentication of certain food products, namely refined oils, may arise when the samples are not fresh. DNA in certain old food samples is prone to damage caused by oxidation (Costa et al., 2012). In other cases when poor quality storage of the DNA containing sample can lead to depurination of the DNA (Elsanhoty et al., 2011).

Sample preparation - Since these biosensors are generally nanoscale, sample size in the range of microlitres is at maximum necessary for adequate testing (Ahmed, 2002; Nugen and Baeumner, 2008). For instance, due to food matrix, obtaining sample sizes that allow for optimum sensitivity is often a mission. Additionally, many of the DNA hybridisation biosensors that have been developed still require a preliminary polymerase chain reaction (PCR) step to be sensitive to traces of DNA or let alone detect specific nucleotide sequences (Hahn et al., 2005). Due to the sensitivity of PCR to inhibitors, extensive sample clean-up is mandatory. Sample clean-up in foods matrix such as those in peanut butter may prove difficult (Nugen and Baeumner, 2008).

Reproducibility and natural integrity of the DNA after purification - For an effective application of all the DNA-based analytical methods discussed in this paper, good quality DNA of great quantity must be available. Accordingly, DNA prior to testing is extracted and purified. DNA extraction and purification methods often prove difficult with possible negative influence in DNA quality and quantity. For instance, the presence of DNA nuclease in food products like olive oil and environmental matter such as mud renders it difficult to extract high quantity DNA of high integrity (Costa et al., 2012; Xiu-Ling et al., 2008; Elsanhoty et al., 2011; Velasco-Garcia and Mottram, 2003).

Refining treatment and processing conditions- DNA-based methods can be affected by failure to detect trace concentrations of DNA in certain products. This can be caused by:

- *Conditions used in processing* - Pro-longed exposure of DNA to heat during thermal treatment and during refining degrade and fragment DNA consequently resulting in DNA of low Integrity. Moreover, pH variations (for example) and the use physical and chemical treatments during processing may randomly break DNA possibly reducing the fragment size of the target DNA sequence (Costa et al., 2012; Elsanhoty et al., 2011).
- *Condition in the final product* - Food products derived from genetically modified organisms may have conditions unfavourable to the stability of DNA caused by the presence of media such as vinegar. Such extreme pHs may result in shortened DNA strands caused by hydrolytically degradation of 3, 5-phosphodiester linkages (Costa et al., 2012; Elsanhoty et al., 2011).

Reference samples - One major limitation of DNA-based analysis is their inability to completely determine unknown DNA sequences. A DNA sequence needs to be predicted or known in advance (Davison and Bertheau, 2007). Even in circumstances where target DNA sequence is known, an appropriate reference is required (Ahmed, 2002). References reduce the measure of uncertainty and form a basis for analytical method validation (Anklam, 1999; Ahmed, 2002; Wu et al., 2009). Due to intellectual property rights obtaining reference samples of some food products is at times impossible (Ahmed, 2002).

4. Future outlook

This review of literature has critically surveyed the state of the art, detailed biosensor concepts and discussed challenges and limitations in

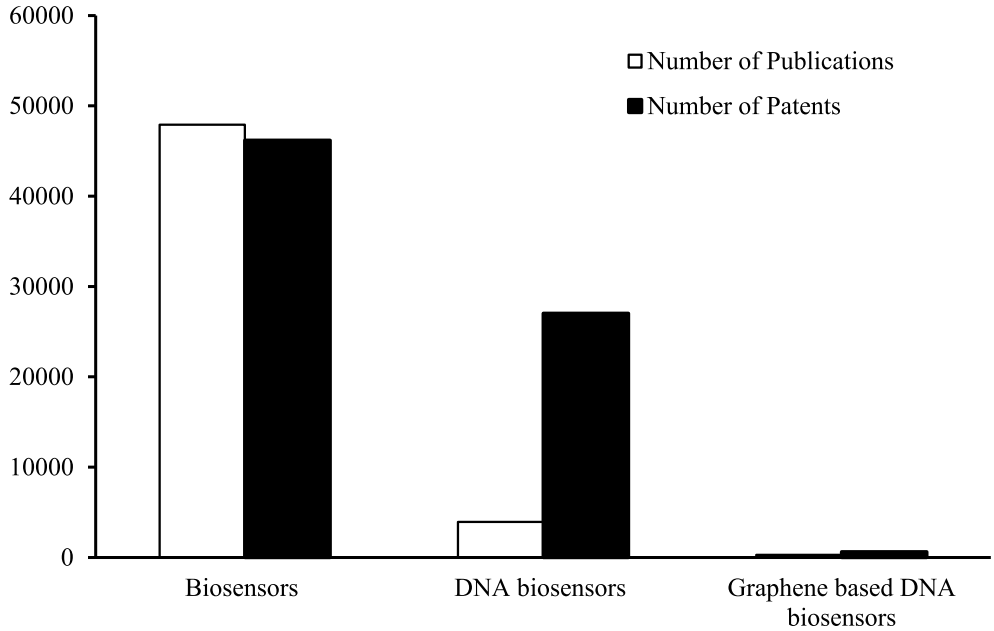

Fig. 10. Bibliometric survey analysis over the period of 1977–2017, using data provided in Scopus of publications and patents related to DNA biosensors.

biosensor development from fundamental and commercial standpoints. Despite challenges and limitations discussed, the number of DNA biosensors patents relative to literature publications is higher (Fig. 10). This enormous registration of patents serves as a model for future possibilities but it has overshadowed the actual commercialisation of biosensors and useful way to dealing with limitation and challenges reviewed. Patents may offer an important financial goal to drive development of biosensors, since the principal developer is not a fundamental scientific researcher, but a commercial company seeking to produce an efficacious device. However, it shifts the dynamics of the biosensors development process towards isolating DNA sensing platforms rather than having a comprehensive understanding of interactions involved in the bio-recognition event and developing innovate methods of evaluations that can produce consistent output signals regardless of the experimental set-up and conditions used.

In the development of DNA biosensor technologies, progress has been made, but only a few have reached the biosensor market (Bora et al., 2013). Reported biosensors are developed and their operation demonstrated in clean-cut laboratory set ups using short oligonucleotides as model targets (Nugen and Baeumner, 2008; Zhang and Hu, 2014). This illustrates implications that a patent driven biosensor development process can have on scientific research. Studies and approaches that simulate and address problems that may arise in real sample conditions remain to be developed. To reach a level of commercialisation that will propel biosensor technologies towards the market, biosensors will require the use of a comprehensive highly accurate analytical parameter such as relative response factor than be used in conjunction with bio-sensing procedures to correct for impurities that can affect the output detection signal of the sensor. This could offer a unique opportunity to a precise measurement of sensitivity and selectivity of the sensor for a given real sample relative to a standard laboratory clean-cut sample. Such an approach can be applied to existing biosensor technologies without compromising the novelty, accuracy and reliability.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sajce.2018.11.002.

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