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Review

Recent advances on functional nucleic acid-based biosensors for detection of food contaminants

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ABSTRACT

It has seen increasing development of reliable, robust, and flexible biosensors for rapid food-safety analysis in the past few decades. Recently, functional nucleic acid-based biosensors have attracted attention because of their programmability, bottom-up characteristics, and structural switches. However, few systematic reviews devoted to categorizing the potential of DNA nanostructures and devices were found for detecting food contaminants. Hence, the applications of functional nucleic acid-based biosensors were reviewed for analyzing food contaminants, including foodborne pathogen bacteria, biotoxins, heavy metals, and et al. In addition to categorizing the various biosensors, multiple signal readout strategies, such as optical, electrochemical, and mass-based signals were also examined. Finally, the future changes and potential opportunities, as well as practical applications of functional nucleic acid-based biosensors were discussed.

1. Introduction

Food safety has become a major challenge with increasing globalization of food industry. Typical foodborne toxins affect the nervous system, DNA damage, and protein synthesis. Causes of food contamination include excessive pesticide and veterinary-drug application, unsanitary production and supply, as well as inappropriate storage. Institutions like the World Health Organization and various nations have categorized food contamination into several groups: chemical, biological, physical, and cross-contamination [1]. Poor food hygiene increases outbreaks of foodborne diseases, with direct effects on public health. According to the World Health Organization, an estimated 600 million people were in poor health after eating contaminated food, and 42,000 die annually [2]. The increasing food safety problems have promoted rapid development and establishment of detection technology and food standards. Newly recognized food components and contaminants are quickly identified, monitored, and quantified [3]. Traditional analytical methods for testing include chromatography [4], mass spectrometry [5], and real-time PCR. However, these methods use expensive equipment, require professional operation, take a long analysis time, and have high maintenance costs. These downsides limit the ability to perform field analyses.

Recently, various biosensors have been widely established as the complementary methods for standard analytical methods, such as enzyme-based, immune-based, thermal, and piezoelectric biosensors. These different read-out types of biosensors depend on nanomaterials for signal output. Different functional nanomaterial-based biosensors for food detection have been widely investigated and reported. These noble the synthesis of metal nanoparticles, carbon nanomaterials, quantum dot, upconversion nanoparticles, metal organic frameworks, and covalent organic frameworks. Biosensors have excellent signal recognition, conduction, and amplification. However, some bottlenecks have occurred with the use of single or composite chemical materials for specific identification and monitoring sensitivity. A vital solution to this problem is to combine novel nanomaterials with specific affinity [6] to increase the speed and sensitivity of detection methods for food contaminants.

Now, DNA is regarded as the nanomaterials as the advancement of automated DNA-synthesis technology. In the 1980s, DNA was used as functional polymers, and these constructions of structural assembly were first proposed by Seeman [7], such as a cube, truncated octahedron, and et al. Besides, the preparation of diverse metal nanoparticle morphologies could be directed to assemble by DNA [8]. Aptamer was first explored by Sullenferet et al. [9] as the functional nucleic acid.

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Subsequently, researchers also developed DNA that had enzymatic function (DNAzymes) [10]. At last, the first functional nucleic acids-based biosensor may occur in the concept of 'molecular beacons' [11], and this type of switch DNA nanostructures opens new biosensing for nucleic acid detection. After that, new developed dynamic structures and functional nucleic acids. In turn, flexible and diverse biosensing modes and platforms became available. In all, functional nucleic acids-based biosensor along with functional nucleic acids and flexible structure devices have opened up the new horizons and been used to develop fast, reliable, and sensitive biosensors of food safety.

Functional nucleic acid-based biosensors can be used to detect multiple types of food contaminants, including nucleic acids, proteins, heavy ions, and other molecules. By altering their structures and inducing different functional assemblies, these biosensors could build intelligent signal transduction through the combination of various DNA structure switches. These switches could induce the conformation with different functional assemblies and produce corresponding signal transduction. The Functional nucleic acid-based biosensors could sense the presence of a designed target analyte through measuring its mass-based properties or signal changes including optical, electrochemical, and mass-based properties.

On the basis of similar topic reviews, it could be divided into two categories: functional nucleic-based biosensors with different signal output methods, and the biosensors with same analysis. The former category is the functional nucleic acid-based biosensor, which could combine with nanomaterials for various signal output methods. For example, colorimetric, fluorescence, electrochemical, and et al. These reviews focused on the signal reading modes or different kinds of targets. Böhme et al. [12] reported the DNA-based tools, assessing the authenticity of food components or products with proteomics, metabolomics, and genomics approaches. The latter is classified according to the same detection targets or same type of functional nucleic acids. Specifically, aiming at typical detection targets, the signal input, signal transformation and signal output of functional DNA were described respectively. Rapini [13] reviewed the aptasensors modified on the screen-printed electrodes between 2016 and 2017, which exhibited great potential for fast response and high sensitivity. Verdian [14] summarized the detection of pesticide residue for aptasensor. In this review, nanomaterial-based aptasensors were classified as optical and electrical biosensors. Xia et al. [15] summed up the aptamer-based homogeneous assays in 2000–2018. These reported aptamer-based methods were analyzed towards structure design, controllability, and nucleic acid amplification. Besides, food safety risk, biosensors, and functional nucleic acid were progressively described by Luo [16]. The nucleic acids were classified as target recognition elements, signal amplification, and 3D nanostructures. This book had a guided significance in the basic theoretical knowledge and methods. However, some related reviews mainly concentrated in early published research articles. These led to many recent research could not be reported in time.

Different from the reported reviews, we mainly aimed to cover the last decade (2010–2020) of progress in improving the detection of food contaminants using functional nucleic acid-based biosensors (Fig. 1). In this review, the role and application conditions of different functional nucleic structures were summarized. Moreover, these corresponding structures were applied with various food contaminations. In particular, the combination of functionalized nucleic acids units to improve the specificity and sensitivity were described. Also, the applications of multiple DNA-based detection methods to food contaminants could increase speed and types of detection targets.

2. Common types of functional nucleic acids used in food contaminant detection

Up to now, several pieces of Online software could predict the secondary structures including Mfold [17] and NUPACK [18]. These programs could predict the secondary structures besides duplex and

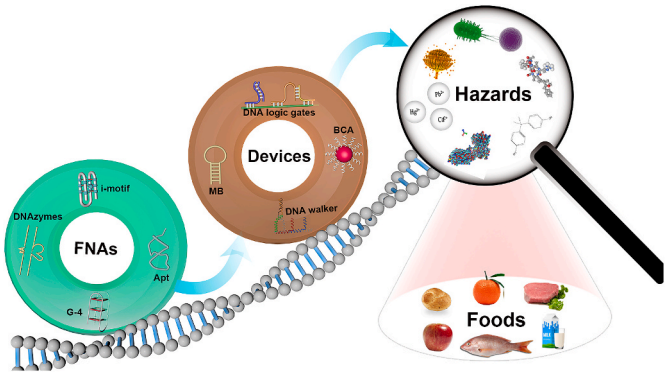

Fig. 1. Application of functional nucleic acids-based biosensors in food contaminants detection.

calculate Gibbs free energy, and we could easily design predicable nanostructures, such as hairpin, double crossover, and holliday junctions. Furthermore, immobile structural DNA was proposed by Ned Seeman [19], including four-arm branched DNA, cubes, and truncated octahedrons. Subsequently, the complex structure of DNA origami was proposed by Rothemund [20], and the technique of DNA origami is a hybridization of hundreds of oligonucleotides with a long M13 single-strand scaffold. This method could be applied to programmable attachment of functional groups, including fluorescent nanoparticles and molecular recognition materials. Hence, functional nucleic acids occurred and filled up the gaps towards the input of DNA biosensors, such as aptamers, DNAzymes, and i-motif. These structures provide the conformation switch when confronted with the external physical, chemical or biological stimulus.

2.1. Aptamers for recognition of food contamination

Aptamers are short single-strand nucleic acids with high affinity and selectivity introduced in 1990 [21,22]. Many screening methods have been developed to accelerate the acquiring of functional aptamers, which could be screened through electrophoresis SELEX [23], magnetic bead-based SELEX [24], cell SELEX [25], and other SELEX methods. Aptamers could recognize and bind to various food contaminants (i.e., proteins, ions, small molecules, and bacteria) because of functional interaction such as stacking of aromatic rings, electrostatic or van der Waals forces, and hydrogen bonding [26]. Moreover, aptamers can be synthesized with high purity and low cost, significantly improving reproducibility of detection methods. More importantly, aptamers also possess the potential for being ingenious and adaptive biosensors with three-dimensional conformational changes that affect binding and dissociation.

Given these properties, numerous aptasensors based on different transduction strategies have been designed in the past decade to identify food contaminants. However, relatively few aptasensors have been practically applied to food safety testing. One reason may be that only a relatively limited number of aptamers are available for food contamination (Table 1). Another reason may be that complex food substrates destabilize aptamer binding ability. Hence, it is beneficial to improve the recognition stability of aptamer by using complex food matrix as the environmental condition for aptamer screening.

2.2. Ribozymes and DNAzymes for specific catalytic activity

Apart from aptamers discovered by artificial screening, RNA enzymes, referred to ribozyme, exhibit the capacity of catalyzing RNAs [48]. Traditional ribozymes play a role in hydrolysis, replication, and ligation in the organism. Many selected methods for the acquisition of artificial ribozymes have been proposed, including in vitro selection

Table 1
Summary of aptamers for food contaminations.

Type	Target	Sequence of aptamer	*Kd* (nM)	Ref
Pathogens	*S.typhimurium*	ATAGGAGTCACGACGACCAGAAAGTAATGCCCGGTAGTTATTCAAAGATGAGTAGGAAAAGAT ATG TGC GTCTACCTCTTGACTAAT	(1.73 ± 0.54)e3	[27]
	L.monocytogens	GGGAGCTCAGAATAAACGCTCAATACTATCGCGGAGACAGCGCGGGAGGCACCGGGGATTCGACATGAGGCCCGGATC	48.74 ± 3.11	[28]
	Staphylococcus aureus	GCAATGGTACGGTACTTCCTCGGCACGTTCTCAGTAGCGCTCGCTGGTCATCCCACAGCTACGTCAAAAGTGCACGCTACTTTGCTAA	61.50 ± 22.43	[29]
	Escherichia coli O111	ATCCGTCACACCTGCTCTACTGGCCGGCTCAGCATGACTAAGAAGGAAGTTATGTGGTGTTGGCTCCCGTAT	NR	[30]
	Norovirus	AGTATACGTATTACCTGCAGCCCATGTTTTGTAGGTGTAATAGGTCATGTTAGGGTTTCTGCG ATATCTCGGAGATCTTGC	18.5	[31]
	Vibrio parahemolyticus	ATAGGAGTCACGACGACCAGAATCTAAAAATGGGCAAAGAAACAGTGACTCGTTGAGATACTTATGTGCGTCTACCTCTTGACTAAT	16.88 ± 1.92	[32]
	Campylobacter jejuni	ACAAGGGACAGTAGACCAACAGGAAAT CAA AGG CCG TGG GAA	292.8 ± 53.1	[33]
	Shigella flexneri	CCTCATGTCGAACAGCAACACTGCAACACTGTATAGTCCTGTGTGCCTTGAGCGTTTATTCTGAGCT	106.4 ± 43.91	[34]
Toxins	*Staphylococcus aureus* enterotoxin B	GGT ATT GAG GGT CGC ATC CAC TGG TCG TTG TCT GTT GTC TGT TAT GTT TCG TGA TGG CTC TAA CTC TCC TCT	NR	[35]
	Staphylococcus aureus enterotoxin A	AGCAGCACAGAGGTCAGATGTACTTATGCATTTCCTCCCACGATCTTATTTGAGAGTGAC CCTATGCGTGCTACCGTGAA	48.57 ± 6.52	[36]
	aflatoxin B1	AGCAGCACAGAGGTCAGATGGTGCTATCATGCGCTCAATGGGAGACTTTAGCTGCCCCCACCTATGCGTGCTACCGTGAA	11.39	[37]
	Ochratoxin A	GATCGGGTGTGGGTGGCGTAAAGGGAG CAT CGG ACA	0.36	[38]
	zearalenone toxin	TCATCTATCTATGGTACATTACTATCTGTAATGTGATATGTT	41 ± 5	[39]
	T-2 toxin	CAGCTCAGAAGCTTGATCCTGTATATCAAGCATCGCGTGTTTACACATGCGAGAGGTGAA GACTCGAAGTCGTGCATCTG	20.8 ± 3.1	[40]
pesticide and veterinary drug residues	Bisphenol A	CCG GTG GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA	8.3	[41]
	Melamine	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	NR	[42]
	Malachite Green	GGAUCCCGACUGGCGAGAGCCAGGUAACGAAUGGAUCC	1	[43]
	Arsenic	GGTAATACGACTCACTATAGGGAGATACCAGCTTATTCAATTTTACAGAACAACCAACGTCGCTCCGGGTACTTCTTCATCGAGATAGTAAGTGCAATCT	4.95 ± 0.31	[44]
	Phorate, profenofos, isocarbophos, omethoate	AGCTTGCTGCAGCGATTCTTGATCGCCACAGAGCT	(0.8–2.5)e3	[45]
	acetamiprid	CTGACACCATATTATGAAGA	4.98 e3	[46]
	mercury ion	thymine−thymine (T−T) mismatches	NR	[47]

NR: not reported.

[49], rational design [50], and computational methods [51]. Similarly, all DNAzymes are artificially obtained and synthesized in vitro SELEX. Considerable attention has been paid to the peroxidase-like activity of DNAzymes [52] in the presence of corresponding metal ions. The most common structures are 10–23 and 8–17 DNAzymes, catalyzing Pb^{2+} [53], Cd^{2+} [54], Mg^{2+} [55,56], UO_2^{2+}, histidine [57], and Na^{+} [58].

Ribozyme and DNAzymes mainly function as the following two aspects: one is regulatory mechanism in food biosensor detection. For example, melamine could trigger triplex formation and activate Mg^{2+}-dependent DNAzymes [59]. The other could also be catalytically amplified. Recently reported peroxidase-mimetic enzymes include AG4, AGRO100, PS2. M, and DAB22. In vitro selection for recognition of *Helicobacter pylori* uncovered a new DHp3T4 DNAzyme [60]. All of these compounds can be used to develop highly sensitive biosensors for metal ions and other small molecules of food contaminants.

2.3. I-motif for pH-responsive biosensors

I-motifs are two parallel-stranded DNA duplexes, formed from cytosine-rich sequences found at the end of telomeres [61]. This specific conformation shows critical regulatory functions in vivo [62], and some researches have focused on applying i-motifs to treatment of cancer cells in pH-responsive systems [63,64]. Mostly i-motifs could incorporate and assemble in other functional nucleic acid units or nanomaterials [65], such as controlled assembly [66], the intelligent conjugated polymer [67], cell imaging [68], and logic operations [69]. However, i-motifs have not received much attention for detecting chemical substances [70]. Furthermore, the potential applications in food safety analysis can be involved, with a new perspective for the construction of biosensor detection method expected to achieve.

3. Various dynamic DNA nanodevices in food-contaminant detection

The kinetics of strand association and dissociation determine the dynamic behavior of nucleic acid nanodevices. Conformational changes mainly depend on the length and secondary structures of ssDNA. This process could be the key to induce strand displacement. Strand displacement can occur between ssDNA and dsDNA when the base sequence of ssDNA homologous to one of the duplex strands. Dynamic strand displacement could produce DNA-circuit signals in response to different inputs. Accordingly, researchers have developed numerous dynamic DNA structures, such as molecular tweezer, DNA walker, and DNA logic gate. Generally, these molecular nanodevices could exhibit controllable operation in responding to external stimuli, resulting in signals and multiple responses. As for the application of food safety detection, most of the DNA nanodevices focused on the targets of heavy metal ions, small organic molecules, nucleic acids and proteins.

3.1. Molecular beacon for intelligent molecular valve

The simplest DNA nanodevice, consisting of the loop and stem structures, could be the molecular beacon. Strong, highly selective target recognition could depend on the design of conformation switch. In Gao's group, a specific "humanoid" molecular beacon was designed by combining with TALEs [71]. In this system (Fig. 2), the stem of molecular beacon was opened with the steric hindrance of the protein, and acted as the signal output for the detection of *Escherichia coli* O157: H7. Zhang [72] developed molecular beacon probes for Hg^{2+} and Pb^{2+} quantitation, incorporating T-rich or G-rich loop sequences into the structure. This process promoted silver deposition using gold nanoparticles, generating a digital readout on the computer. Generally, molecular beacons could be employed to colormetric, fluorescence, SERS, and other optical sensing strategies.

3.2. DNA logic gate devices for multiplex detection

DNA logic gates were first introduced in 2004 [73]and emerged as a new logic system. Compared with semiconductor-based systems, the DNA logic gate would not be confined to electron transfer. The DNA logic gate could be triggered by different types of stimulation, and produce the corresponding signals as the output. This device is divided into three parts: input strands for receiving external stimuli, transformation strands for signal processing, and output strands for signal reception. Wang et al. [74] constructed a GO/aptamer logic detection system. Through the 'or' and 'inhibit' logic gates, the fluorescence intensities of 5-carboxyfluorescein could be regulated. Combinations of Boolean operations have also been integrated into these DNA logic gate devices, generating multiplex gates that released a variety of outputs. Moreover, these developed molecular systems could respond to different external stimuli, releasing multiple signal outputs. Hence, DNA logic gates have the potential to expand the applications, ranging from mathematical function to biological detection. In terms of food safety, the logic gate system could be applied to detection and screening for

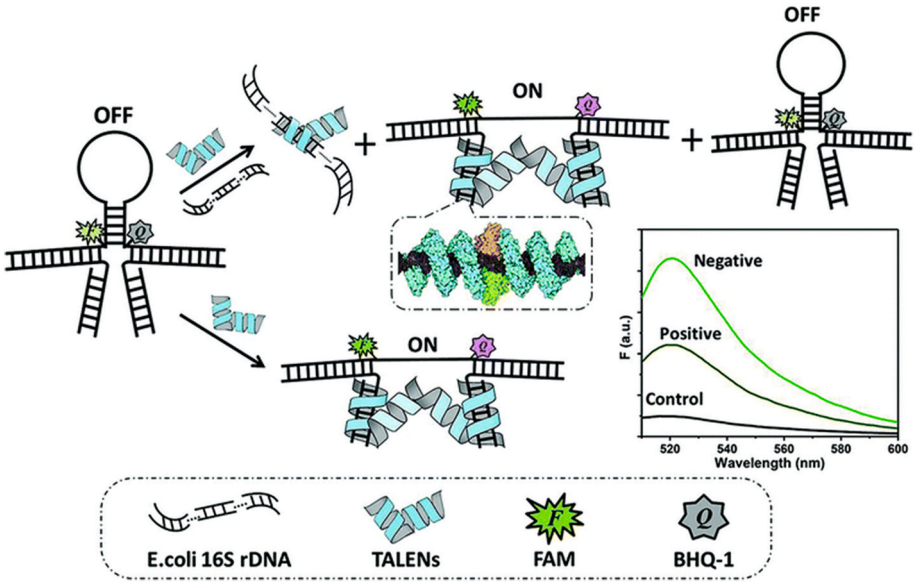

Fig. 2. MBs used for deteciton of *Escherichia coli* O157: H7; Reproduced from Refs. [66]with permission. Copyright 2018 Royal society of chemistry.

multiple targets.

3.3. DNA walkers for dynamic nanodevices

Thus far, static nanodevices of functional nucleic acids have been stated above. In contrast, DNA walkers are dynamic tools useful for mediation of diverse signals, including 1D, 2D, and 3D tracks. The functional structural units of DNA walkers consist of three components (Fig. 3), including a walker, a track and fuel molecules or other forms of energy input that drive the motion [75,76]. Successive strand hybridization and displacement is one type of driving force. Nucleases (e.g., DNAzyme [77,78], nicking endonuclease [79], and exonuclease [80, 81]) are also candidates to assist direct and autonomous movements. The special motion in DNA walkers could be applied to signal transduction and amplification. For example, Yang et al. [82] constructed the detection of aflatoxin B1 in food matrixes through DNA walking machine for signal probe separation and motion on the electrode. Aflatoxin B1 triggered DNA hybridization to release an anti-aflatoxin aptamer. A Pb^{2+}-specific DNAzyme was then activated to cleave substrate DNA, which obviously increased the redox currents. The available research on DNA walker devices suggests they will be valuable biosensor tools for on-site detection of food contaminants.

3.4. Nucleic acid signal amplification

Ultrasensitive detection of food contaminants is meaningful and necessary. Despite various functional materials and methods as signal amplification, the nucleic acid can also act as signal amplifiers through the advantage of density, thus amplifying the detection signal. Typically, polymerase chain reaction (PCR) was first applied as amplification technology for the detection of low-abundance nucleic acids and other targets. Traditional classic detections of foodborne pathogens, consisting of *Escherichia coli* O157, *Salmonella*, and *Staphylococcus aureus*, were provided through standardized PCR methods [83]. However, this variable temperature technology requires precise thermal cyclers and specific enzymes, limiting the practical application in outdoor environment. Recently, isothermal amplification, which can detect a broad spectrum of food contaminants, including bacteria, viruses, proteins, and small molecules. Meanwhile, depending on the density advantage of DNA coated on the surface of nanoparticles, the bio-barcode technology also has been proposed.

3.4.1. Isothermal amplification of nucleic acid technique

Isothermal amplification is low-cost, efficient, and easy to perform because it does not require thermo cycling equipment. Isothermal amplification could be achieved in constant temperature including loop-mediated isothermal amplification [84], hybridization chain reaction [85], rolling circle amplification [86], catalytic hairpin assembly [87], and other amplification techniques. These enzyme-based amplification systems could perform exponential and linear kinetic reactions. For example, traditional loop-mediated isothermal amplification with *bst* polymerase, could specifically amplify a few copies of DNA to $>10^9$ copies. Another method capable of exponential reactions is rolling circle amplification, which formed a long DNA through chain with Phi 29 DNA polymerase assisting. Through multiple primers, hybridization with a circle template produced various rolling circle amplification products [88]. On the contrary, the original enzyme-free amplification, hybridization chain reaction and catalytic hairpin assembly, could generally exhibit linear kinetic reactions. HCR exhibited the signal amplification in different platforms of biosensing. Both of them showed the simple, enzyme-free amplification, and structural flexibility advantages. Besides, multiple cascaded isothermal amplifications have been developed for detection of pathogenic bacteria and viruses, which amplify the specific gene sequences. Notably, many researchers have focused on applying isothermal amplification devices to universal biosensors. Hence, in this new biosensor system, the DNA is used as the read-out probes and combination of isothermal amplification of nucleic acid for enhancing the sensitivity.

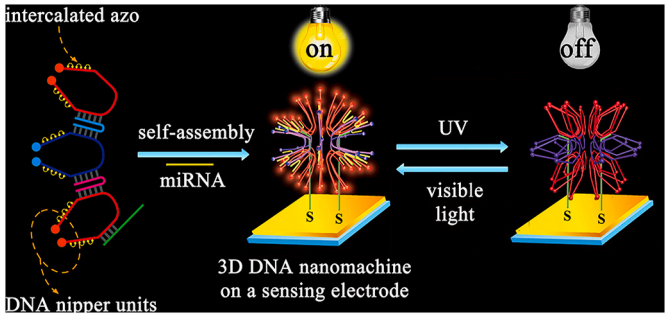

Fig. 3. Field-Free 3D DNA Nanostructure for single-step sensing; Reproduced from Refs. [71]with permission. Copyright 2018 American Chemical Society.

3.4.2. Bio-barcode assay

Unlike nucleic acid amplification, the bio-barcode assay amplifies the output signal by depending on the number of nucleic acid-coated on the surface of nanomaterials, mostly gold nanoparticles, polystyrene microsphere, and other spherical nanoparticles. Proposed by Mirkin [89], the bio-barcode assay was first applied to ultrasensitive detection of biomarkers, such as prostate-specific antigen [90], amyloid-β-derived diffusible ligands [91], and α-fetoprotein [92]. The development of bio-barcode assay mainly focused on two aspects: One is the expansions of detection platforms. Traditional spectral responses [93,94] have expanded to electrochemical [95], MALDI-TOF (Fig. 4) [96], and electrochemiluminescence [97] methods. The other is the cascade signal amplification. Although traditional bio-barcode assay could realize trace detection as low as pg level, it is difficult to achieve accurate quantification of target. Adding isothermal nucleic-acid amplification increased sensitivity and detection range. Based on this concept, Zhang et al. [98] developed a bio-barcode and rolling circle amplification assay for detecting T-2 toxin. Such ultrasensitive techniques with multiple barcode DNA probes could be applied to detecting food contamination.

4. Applications of functional nucleic acid-based biosensors in food analysis

Due to the complexity of food contaminants, the DNA-based biosensing methods could be distinguished from various targets (Table 2). However, these detection methods could be measured according to the change of optical spectrum with colorimetric, fluorescence, and surface-enhanced raman scattering. Besides, electrochemical, and mass-based properties are also included.

4.1. Foodborne pathogen bacteria

Foodborne pathogen bacteria exist in the food substrate for reproduction and take up 66% in the main causes of food poisoning [99]. In 2018, the Food and Drug administration announced that about 207 million eggs were infected with *Salmonella* [100]. In China alone, the Chinese National Health Commission reported 5926 cases of foodborne illness in 2015, with 3181 cases stemming from pathogenic bacteria (e.g., *Cereus*, *Clostridium perfringens*, *Campylobacter jejuni*, and *Legionella* spp.) [101]. Traditional bacterial detection methods (e.g., microbial cultures, ELISA) are time-consuming, tedious, and error-prone (both false-positives and false-negatives). Molecular detection approaches have been proposed to combat these issues [102], including novel nucleic-acid amplification technology that can amplify specific bacterial sequences [103]. Nevertheless, the initial versions suffered from cross-reactivity and low-sensitivity.

Thus, development of functional nucleic acid-based biosensors aims

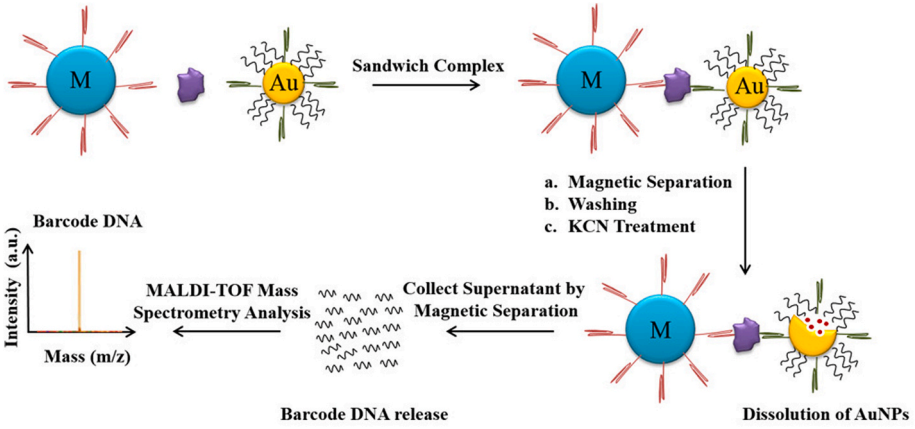

Fig. 4. The bio–barcode assay method Reproduced from Refs. [91]With permission. Copyright 2003 Science.

Table 2
Functional nucleic acid-based assays for food contamination.

Functional nucleic acid module	Analyte	Assay	LOD	Recovery Rate	Refs
Aptamer	S. Typhimurium	Fluorometric	20 CFU ml^{-1}	–	[102]
Aptamer	*Escherichia coli*	Electrophoresis	370 CFU ml^{-1}	92.8–94.7%	[108]
Aptamer	*E. coli& S. aureus*	SERS	20 and 50 cell ml^{-1}		[109]
Aptamer	*E.coli* O157:H7	impedimetric	100 CFU ml^{-1}	–	[110]
ERA	*S.Typhimurium*	fluorometric	9.86 CFU ml^{-1}	96.8–103.7%	[112]
Aptamer & DNAzyme & EXTRA	*S.Typhimurium*	colormertic	80 CFU ml^{-1}	93.8–102.6%	[113]
MBs & DNAzymes & SDA	*S.Typhimurium*	fluorometric	8 CFU ml^{-1}	–	[114]
asymmetric PCR	*E.coli* O157:H7&*Listeria innocua*&*S. aureus*	electrophoresis	1 pg ml^{-1}	–	[115]
Aptamer & CHA	Aflatoxin M1	fluorometric	0.01 ng ml^{-1}	91.9–109.2%	[118]
Aptamer	Aflatoxin M1 & Ochratoxin A	fluorometric	1.48 and 15.4 pg ml^{-1}	–	[119]
Aptamer	Ochratoxin A	electrochemical	3.3 pmol ml^{-1}	95.7–100.18%	[120]
Bio-barcode & PCR	*Staphylococcus aureus* enterotoxin B	fluorometric	0.269 pg ml^{-1}	89.17–110.29%	[121]
aptamer	abrin toxin	chemiluminescence	1 nmol ml^{-1}	–	[124]
T-Hg2+-T	Hg^{2+}	electrochemical	0.08 nmol ml^{-1}	96.4–103.0%	[136]
ssDNA	Hg^{2+}	fluorometric	3 nmol ml^{-1}	85.05–103.51%	[137]
G-quadruplex	Pb^{2+}	fluorometric	10 pmol ml^{-1}	88–105%	[138]
Aptamer	acetamiprid	colorimetric	89.8 μmol ml^{-1}	–	[142]
Aptamer &*Dpn*II&EXO III	ampicillin	electrochemical	32 nmol ml^{-1}	94–105.4%	[144]
split G-quadruplex& strand displacement	17β-estradiol	colorimetric	1 pmol ml^{-1}	–	[145]
Aptamer & HCR &nicking endonuclease	PCB72/106	fluorometric	0.35 pg ml^{-1}	93.4–109.7%	[147]

to improve molecular recognition and signal conversion. Target recognition depends on aptamers that bind with bacteria. Currently, aptamers have been identified for common bacteria, such as *Samonella enterica* Typhimurium [104], *Escherichia coli* O157:H7 [105], *Staphylococcus aureus* [106], and *L. monocytogenes*. Aptamers are substitutes for antibodies used in immunoassay technology such as ELISA. Shin et al. [107] developed an aptamer-based sandwich assay to detect *Salmonella enterica* ser. Typhimurium. This sandwich method used a dual-aptamer for recognition and capture, which exhibited a linear quantitative relationship. Zhang et al. created a fluorescence detection system via combining microchip capillary electrophoresis with *anti-Escherichia coli* aptamer for achieving fluorescence detection [108]. The same research group also developed dual SERS-tags labeled with aptamers [109]. His research investigated *Escherichia coli* and *Staphylococcus aureus* as detection bacteria, using vancomycin-modified Fe_3O_4@Au MNPs to capture the gram-positive bacteria and aptamer-modified AuNPs as specific SERS tags. At last, the dual Raman signal tags could be detected in response to *Escherichia coli* and *Staphylococcus aureus*. Brosel-Oliu et al. [110] proposed an impedimetric aptasensor for detection of *Escherichia coli O157:H7*. In their work, the aptamer was used to recognize the outer membrane proteins of *Escherichia coli* O157:H7 through electrochemical impedance spectroscopy technique. Still other detecting methods could be captured by the cell wall binding domains, while DNA-programmed signal amplification lowered the limit of detection. For instance, Seok-Joon et al. [111] used CBDs to recognize and enrich the *Staphylococcus aureus*, *Bacillus anthracis*-Sterne, and *Listeria innocua*. After that, qPCR of specific DNA barcodes could complete quantify the target bacteria. Up to now, numerous strategies have been developed that combined aptamers with DNA nanodevices. A fluorescence biosensor for detection of pathogenic bacteria based on target-triggered enzymatic repairing amplification (ERA) was developed by Leng et al. [112]. A primer first blocked the aptamer of *Salmonella enterica* Typhimurium, and the ERA amplification was triggered only in the existence of the primer. A similar colorimetric assay of *S. Typhimurium* [113] through aptamer-triggered exponential amplification reaction was coupled with DNAzyme. Besides, the target bacteria could be substituted for their specific sequences. Leng et al. [114] described a fluorometric strategy through the combination of target-modulated photo-induced electron transfer between G-quadruplex DNAzymes and DNA, with the hairpin probe-based circular exponential amplification. Moreover, multiplex detection of pathogenic bacteria through asymmetric PCR was applied to paper-based biosensor [115]. Genomic DNA biosensor system [116] with a sandwich structure could successfully detect *Staphylococcus aureus*. Despite these promising strategies, the functional nucleic acids-based biosensors have been rarely applied to detect foodborne pathogens [117]. To develop novel methods for monitoring food contamination, structural performance and binding fundamentals of DNA should be focused. Traditional immunological sensors should be introduced into the sensing method in the aspect of analytical steps and optimization of reaction conditions.

4.2. Biotoxins

Food biotoxins, ranging from microbial toxins to phytotoxins, originate from plants, animals, fungi and other organisms. In many countries, the processing, storage, and transportation of foods could be contaminated, and produced varies of biotoxins. In particular, the bacteria and fungus could spread via air, water, or soil. Microbes typically grow on various food substrates stored under appropriate environmental conditions. Heath costs vary depending on toxin type, exposure, and entry route. The identification and detection of food toxins have been used to monitor the risk of food poisoning.

Among all the biotoxins, mycotoxins are the major contaminants produced by fungi and bacteria. Of particular agro-economic importance are aflatoxins, ochratoxins, zearalenone, fumonisins, deoxynivalenol and other trichothecenes. Recently, functional nucleic acids-based biosensors provided a novel way to detect mycotoxins. Guo et al. [118] proposed a simple and low-cost assay for sensitive and specific detection of aflatoxin M1. After the aptamer binded with the aflatoxin M1, the released primer would trigger the CHA reaction and form G-4 structure. In turn, the G-4 structure could enhance the *N*-methyl-mesoporphyrin fluorescence to visually indicate aflatoxin presence. Multiplex mycotoxins (aflatoxin B1 and ochratoxin A) detection have also been developed. A new aptamer microarray was capable of both mycotoxins [119], and the TiO_2 was modified on the surface of porous silicon through spinning sol-gel. The formation of nano-TiO_2 layer could raise the fluorescence intensity compared with traditional thermally oxidized porous silicon. Yang et al. [120]prepared aptamer/NH_2 Janus particles for developing a novel electrochemical aptasensor. One side of the janus particles belong to glassy carbon through peptide bond. The other was functionalized with *anti*-ochratoxin A aptamer for specific detection. Furthermore, Xu et al. [121] realized ultrasensitive detection of Staphylococcal enterotoxins B through the bio-barcode assay. In this strategy, the *anti*-SEB modified MMPs could capture the SEB in the detection system. AuNPs were modified with goat *anti*-SEB polyclonal antibody and DNA barcodes. In the presence of SEB, both probes then created a sandwich structure through antigen-antibody interactions. Consequently, the SEB target could be indirectly quantified by real-time PCR, which corresponded to the number of DNA barcodes.

Besides the myotoxins, some plant-derived toxins (phytotoxins) could be found in both proceed and untreated foods, which are difficult to digest. For instance, morphine is present in poppy seed soil, and overdose could cause asphyxia [122]. The ricin and abrin toxin are present in castor beans and rosary peas, respectively. Acted as the type 2 ribosome-inactivating protein, both lead to cell death and cannot be diagnosed. It is meaningful for the detection of them in adulterated food and beverages. Men et al. [123] presented an aptasensor method by combining g–C_3N_4–MnO_2 nanosheet with liposome amplification. Tang et al. [124] isolated a specific aptamer to recognize abrin toxin, then developed a direct chemiluminescence assay with a light switching reagent ($[Ru(phen)_2(dppz)]^{2+}$). Ahmadi et al. designed an engineered stabilized DNA switch. This strategy contained two complementary sequences (cDNAs) and an *anti*-patulin aptamer. The two cDNAs separated in the presence of different concentrations of patulin and showed a ratio fluorescence signal intensity [125].

Additionally, animal toxins, such as tetrodotoxin and saxitoxin, were less frequently reported. Recently, a temperature-assisted fluorescent biosensor was recently developed to detect saxitoxin by Cheng et al. [126]. The aptamer-saxitoxin complex could decrease the melting temperature, in turn inducing the temperature-assisted fluorescence resonance energy transfer method. From the described results above, the functional nucleic acids-based biosensor could be applied in biotoxin determination. However, many biotoxins identification have not been investigated and multiplex detection methods are uncommon. There is room to further advance the applicability of such biosensors in biotoxin detection.

4.3. Heavy metals

Heavy metals have recently spread into the food chain with the development of the food industry and environmental pollution. Typical heavy metals, including mercury [127], arsenic, cadmium and lead [128]. The bioaccumulation of heavy metals leads to a vicious spiral in all animals. Excessive exposure to the mercury, especially methylmercury (MeHg), harms the central nervous system and the kidneys [129].

The most common methods for heavy-metal detection are inductively coupled plasma mass spectrometry (ICP/MS) [130], Atomic absorption/emission spectroscopy (AAS/AES) [131,132], ICP-AES [133], and ICP-optical emission spectrometry [134]. Although these methods mentioned above exhibit high sensitivity and selectivity. However, the on-site detection capacity is limited. Existing functional nucleic acids-based biosensors have the promising potential to detect heavy metal ions. Specifically, artificial DNAzymes and aptamers could selectively bind with metal ions. These types of "DNAzymes/heavy metal ions" binding led to the changes of structure and functions, which could convert to measurable signals through the analytical devices. The selective binding of heavy metal ions could switch the stable duplex DNA structures and change the generation of the measurable signal response. For example, T-Hg^{2+}-T mismatches [135] has been used as Hg^{2+} detection biosensors based on their ability to stabilize two complementary single-strand DNA. A novel ratiometric electrochemical strategy [136] involved hybridization of methylene blue with a T-rich ferrocene-labeled DNA probe in the presence of Hg^{2+}. Then, the molecular beacon tags were then repelled from the gold electrode surface, while ferrocene tags draw closer. These conformation changes decreased the beacon's oxidation peak current as the content of ferrocene increased. Another rapid Hg^{2+} detection method [137] used label-free single-strand DNA and SYBR Green I. The latter embedded into the grooves of double-helix structure only in the presence of Hg^{2+}, generating strong fluorescence. For Pb^{2+} detection, a promising method [138] used G-quadruplex as the signal report probe that bound with *N*-methyl mesoporphyrin IX (Fig. 5). This special DNAzyme had catalytic properties when combined with Pb^{2+} [139]. Hence, the selective recognition of DNAzyme could be designed to detect Pb^{2+}. Mechanistically, in the absence of Pb^{2+}, the enzyme-oligonucleotide strand could hybridize with the substrate strand. The presence of Pb^{2+} catalyzed ribonucleic acid sites and dissociates the two ssDNA. This structural transformation was detectable and the basis for applications as a biosensor. Similarly, Li et al. [140] developed a fluorescence method for Pb^{2+} detection through a G-quadruplex DNAzymes (AGRO100). Another group developed a colorimetric detection kit for food samples [141]. In this strategy, Pb^{2+}

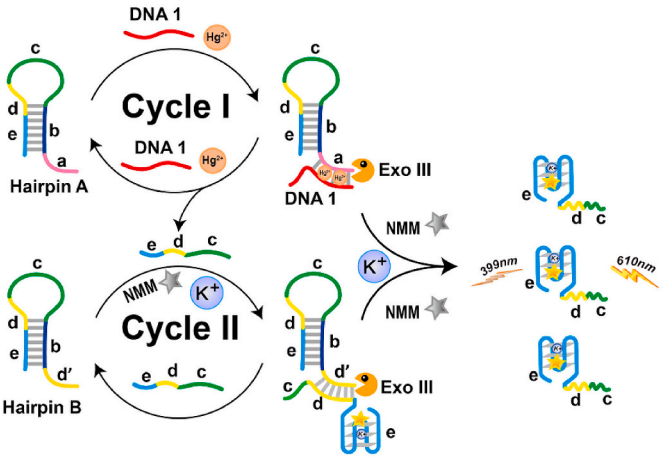

Fig. 5. Exonuclease III and G-quadruplex DNAzyme were used for the detection of Hg^{2+}. Reproduced from Refs. [133] With permission. Copyright 2020 Elsevier.

enabled the formation of G-rich nucleic acids that catalyzed the H_2O_2-mediated oxidation of colorless guaiacol. In all, the functional nucleic acids-based biosensors showed a promising application for sensitive and rapid detection of heavy metal ions in foods. Besides, many functional nucleic acid structures and nanomaterials were incorporated in the structure-switch changes, thus improving the stability and sensitivity of biosensor. However, ion interference may increase the background values and easily reduce the activity of nucleic acid exonuclease enzymes. Currently, laboratory experiments have not demonstrated an ability to simultaneously detect multiple heavy metal ions. In this situation, dynamic DNA walker and logic gates may provide the possibilities for sensing multi-level output signals.

4.4. Pesticide and veterinary drug residues

Pesticide and veterinary drug residues are heavily used in modern agriculture, leading to food contamination by their residues. Many countries mandatory have enacted the relevant regulations and standards to limit minimum residues, especially in China. Presently, the most widely studied veterinary drugs in terms of food safety are tetracycline and chloramphenicol antibacterial agents. The demands for rapid and multi-residue detection are increasing, and the biosensors have occurred in residues detection. Jokar et al. [142] reported a colorimetric aptasensor assay that generated LSPR properties in Ag nanoparticles when acetamiprid was present and interacted with the aptamer. Signals from the transformation were detectable through ultraviolet–visible spectroscopy. Another electrochemiluminescence detection method was developed for the pesticide aldicarb [143]. Here, sixth-generation poly (L-arginine) dendrimer/multiwalled carbon nanotubes were modified on the surface of the electrode. AuNP-tagged aptamers were linked to a glassy carbon electrode, developing a switch-type aptasensor. Similarly, in Yin's group, an electrochemical aptasensor was established for detection of ampicillin. In the absence of the antibiotic, a *Dpn*II recognition site was stimulated without the ampicillin and subsequently the residual dsDNA fragment was digested by the EXO III. The resultant decreased in electron transfer increases the electrochemical signal [144].

Besides, partial industrial pollutants, such as 17β-estradiol, bisphenol A, polychlorinated biphenyls and et al., have a significant impact on food safety. The detection of 17β-estradiol had been proposed through a three-way G-quadruplex junction sensing system. In the functional nucleic acids-based biosensor, Chen et al. [145] combined the split G-quadruplex with toehold-mediated strand displacement, reducing the detection concentration to 1 fM. Li et al. [146] reported an aptasensor method based on fluorescence resonance energy transfer. The streptavidin modified UCNPs could bind to biotin-labled bisphenol A aptamer. Meanwhile, the 5-carboxytetramethylrhodamine modified cDNA could induce fluorescence resonance energy transfer through the combination of bisphenol A aptamer and cDNA. Wang et al. [147] developed a novel nucleic acid amplification method to detect PCB72/106 (Fig. 6). This method combined the hybridization chain reaction with nicking endonuclease, to acquire the maximum efficiency of fluorescence intensity. Jiang et al. addressed a SERS-based aptasensor for ultrasensitive detection of kanamycin. Sulfo-cyanine3 was used as Raman reporter with a characteristic Raman band at 1590 cm^{-1}. In the presence of kanamycin, sulfo-cyanine3 was released from the surface of Au@Ag NPs, causing a visible drop of SERS signal [148]. In all, pesticide, veterinary drug residues and other industrial pollutants are usually small molecules. Their detection encountered several difficulties, including low binding interactions with functional acid and small binding sites. To address these problems, we recommend the development of split-molecular structures or novel nanomaterial that could improve sensitivity.

5. Conclusion and future prospects

In this review, the functional nucleic acids-based biosensors were discussed with different functional DNA incorporating with various nanodevices. DNA nanostructures exhibit multiple conformational changes in the presence of different stimuli. Thus, they are suitable biosensor platform and the source for developing practical bioassays. We also described the remarkable progress of functional nucleic acids-based biosensors as food contaminants detection system. Researchers have applied them to foodborne pathogenic bacteria, biotoxins, heavy metals and pesticide and veterinary drug residues. The combination of DNA nanodevices with advanced nanomaterials have achieved considerable sensitivity, specificity, and efficiency in the stage of laboratory.

Despite their advantages, there are still some challenges towards on-site detection. First, owing to the complex food matrix, the functional nucleic acids-based biosensors have faced some obvious defects towards practical applications. Different food components, including sugars, ions and proteins, could interfere the signal recognition, leading to false-positive results. Second, most applications involve single target detection, and few studies have made full use of nucleic acid structures to

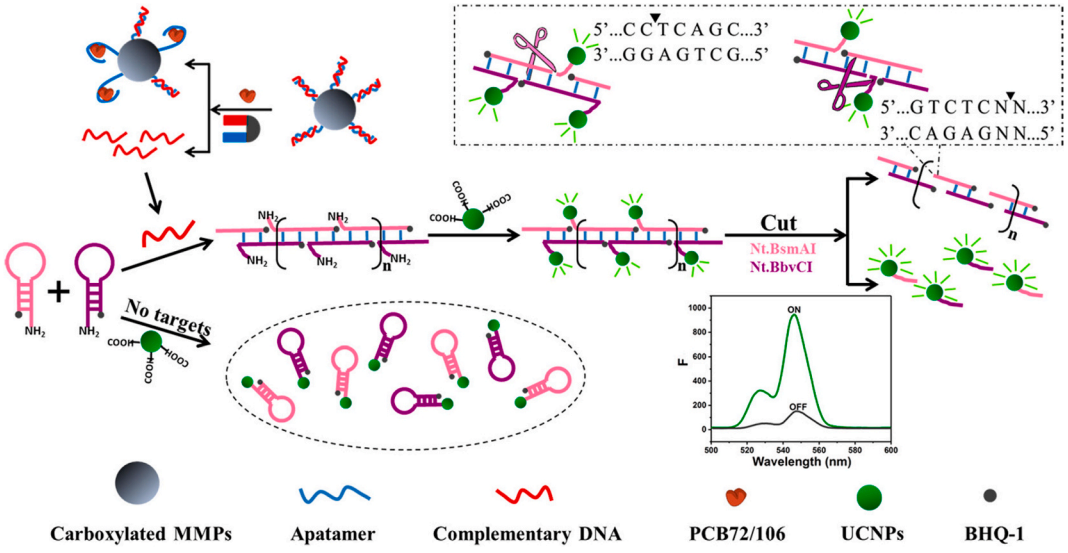

Fig. 6. A novel nucleic acid amplification method for detection of PCB72/106 through dual amplification strategy. Reproduced from Refs. [142] With permission. Copyright 2018 American Chemical Society.

develop multiplex detection methods. Third, we have only identified a limited number of aptamers for specific binding, and have been lack of theoretical research in specificity and anti-degradation. Therefore, future development could be recommended the following three areas:

(1) The functional nucleic acids-based biosensor should be combined with sample pretreatment for further development. For example, we could establish host-guest recognition through functionally advanced materials, or post-modification of bio-recognition molecules. In all, functional nucleic acids-based biosensor is expected to integrate to form a set of integrated separation and detection through sample pretreatment.
(2) Multiple food contaminations screening should be developed with the incorporation of DNA logic gates and DNA walker as the autonomous dynamic DNA nanodevices. Currently, RNA-guided enzymes, referred to clustered regularly interspaced short palindromic repeats proteins, have been used for detection of small molecules. The combination of RNA-guided proteins with functional DNA structures could be capable of detecting partial food contaminants. Besides, nucleic acid hydrogel and DNA origami can also be used for components of multiple detection in the future. At last, the designer of functional nucleic acids-based biosensor should be better compatibility with point-of-care detection. Lab on a chip could be the way to realize the real application of functional nucleic acids-based biosensor.
(3) Novel characterization methods, such as cryo-STEM, should be employed to analyze the precise structure of nucleic acid. These new characterization techniques could improve the reliability and accuracy of the functional acid-based detection. Also, further chemical thermodynamics model should be examined in nucleic acid interaction with proteins/small molecules.
(4) From the perspective of different detection targets, some heavy metal ions detection methods could further conduct the standardization research, owning to the excellent sensitivity and specificity. Foodborne pathogens have abundant recognition sites that are ideal for “sandwich” DNA biosensor detection. Lastly, we need to develop methods that can improve the specificity of biotoxins, agricultural and veterinary drugs possess many small molecular structure analogues detection.

Declaration of competing interest

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

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