Biosensors and Bioelectronics 130 (2019) 174–184

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

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

Aptasensors for pesticide detection

Mei Liu[a,b], Arshad Khan[a], Zhifei Wang[b], Yuan Liu[a], Gaojian Yang[c], Yan Deng[a,c,*], Nongyue He[a,c,*]

[a] State Key Laboratory of Bioelectronics, National Demonstration Center for Experimental Biomedical Engineering Education (Southeast University), School of Biological Science and Medical Engineering, Southeast University, Nanjing 210096, PR China
[b] School of Chemistry and Chemical Engineering, Southeast University, Nanjing 211189, PR China
[c] Economical Forest Cultivation and Utilization of 2011 Collaborative Innovation Center in Hunan Province, Hunan Key Laboratory of Biomedical Nanomaterials and Devices, Hunan University of Technology, Zhuzhou 412007, PR China

ARTICLE INFO

Keywords:
Aptamer
Biosensor
Aptasensor
Pesticide
Detection

ABSTRACT

Pesticide contamination has become one of the most serious problems of public health in the world, due to their wide application in agriculture industry to guarantee the crop yield and quality. The detection of pesticide residues plays an important role in food safety management and environment protection. However, the conventional detection methodologies cannot realize highly sensitive, selective and on-site detection, which limits their applications. Aptamers are short single-stranded oligonucleotides (RNA or DNA) selected by SELEX method, which can selectively bind to their targets with high affinity. Compared with the commonly used antibodies or enzymes in designing biosensors, aptamers exhibit better stability, low molecular weight, easy modification and low cost, and were regarded as excellent candidates for developing aptasensors for pesticide detection. In this review, application of aptamers for pesticide detection was reviewed. Firstly, aptamers specifically bind to various pesticides were first summarized. Secondly, the progresses and highlights of developing aptasensors for highly-sensitive and selective detection of pesticide residues were systematically provided. Finally, the present challenges and future perspectives for developing novel highly-effective aptasensor for the detection of pesticide residues were discussed.

1. Introduction

Nowadays, pesticide contamination has aroused much public attention due to the widely utilization of pesticides in agriculture for the purpose of increasing crop yields and improving the quality of agricultural products (Eddleston et al., 2008; Songa and Okonkwo, 2016; Yan et al., 2018). However, the abuse of pesticides has also caused serious food and environment contamination, and has become one of the most alarming challenges in public health in the world (Carvalho, 2017; T.J. Li et al., 2018; K.K. Liu et al., 2016). It was estimated that there were millions of people got poisoned with pesticides and more than 300,000 people died from pesticide poisoning every year all over the world (Lekei et al., 2016; K.K. Liu et al., 2016; Pedersen et al., 2017; Safaa, 2011). Therefore, to reduce pesticide poisoning and establish proper management of pesticides, amounts of policies have been established by the governments for guiding the utilization of pesticides and thereafter various maximum residue levels in foods and agricultural products were determined. Although certain effects have been achieved on the management of pesticide poisoning and residues monitoring, pesticide contamination remains a tough public challenge that threatens human health and survival. Pesticide residue detection is a key approach for the management of pesticide contamination, which requires development of new novel methods for highly-sensitive detection.

In the past years, various methods for the detection of pesticide residues were developed, including conventional methods and novel biosensors. The conventional methods for the detection of pesticide residues such as high-performance liquid chromatography (Montemurro et al., 2016; Obana et al., 2002; Yang et al., 2015), mass spectrometry (Christodoulou et al., 2018; X.Z. Wu et al., 2018; Zhong et al., 2016), gas chromatography (Xu et al., 2014; Zhan et al., 2017), and their combined applications were demonstrated to be very effective and fairly accurate, and thus were regarded as gold principles for the detection of pesticide residues (L. Lan et al., 2017; Xu et al., 2017). However, those methods for the detection of pesticide residues are always limited because they are very complex, time and labor consuming, need tedious sample pretreatment and expensive equipment, and also need professional workers (Songa and Okonkwo, 2016). Besides,

* Corresponding authors at: State Key Laboratory of Bioelectronics, National Demonstration Center for Experimental Biomedical Engineering Education (Southeast University), School of Biological Science and Medical Engineering, Southeast University, Nanjing 210096, PR China.
E-mail addresses: hndengyan@126.com (Y. Deng), nyhe@seu.edu.cn (N. He).

https://doi.org/10.1016/j.bios.2019.01.006
Received 21 November 2018; Received in revised form 5 January 2019; Accepted 12 January 2019
Available online 15 January 2019
0956-5663/

Table 1
Available aptamers specifically for pesticide residue detection.

Target	Sequence	Kd (nM)	Reference
Carbendazim	GGGCACACAACAACCGATGGTCCAGCCAC CGAATGACCAGCCCACCCGCCACCCCGCG	65 nM	(Eissa and Zourob, 2017)
Fipronil	TGTACCGTCTGAGCGATTCGTACAGTTTCTGGAGGACTGGGCGGGGTGACGGTTATGAGCAGTCAGTGTTAAGGAGTGC	48 ± 8 nM	(Hong and Sooter, 2018)
Fluoroacetamide	ACCTGCAGGCGCGAGTTTCAGATCAAAACTTGTCTGGCGT and GGCGTGTGCCCTGCGGA TGAAGACTGGTCT	1 and 1.2 μM	(Cao et al., 2016)
Acetamiprid	TGTAATTTGTCTGCAGCGGTTCTTGATCGCTGACACCATATTATGAAGA	4.98 μM	(He et al., 2011)
Phorate	AAGCTTGCTTTATAGCCTGCAGCGATTCTTGATCGGAAAAGGCTGAGAGCTACGC	1.11 μM	(Wang et al., 2012)
Profenofos	AAGCTTGCTTTATAGCCTGCAGCGATTCTTGATCGGAAAAGGCTGAGAGCTACGC	1.0 μM	(Wang et al., 2012)
Isocarbophos	AAGCTTGCTTTATAGCCTGCAGCGATTCTTGATCGGAAAAGGCTGAGAGCTACGC	0.83 μM	(Wang et al., 2012)
Omethoate	AAGCTTTTTTGACTGACTGCAGCGATTCTTGATCGCCACGGTCTGGAAAAAGAG	2.0 μM	(Wang et al., 2012)
Atrazine	TGTACCGTCTGAGCGATTCGTACGAACGGCTTTGTACTGTTTGCACTGGCGGATTTAGCCAGTCAGTGTTAAGGAGTGC	0.62 ± 0.21 nM	(Williams et al., 2014a)
Edifenphos	CGTACGGAATTCGCTAGCTAAGGGATTCCTGTAGAAGGAGCAGTCTGGATCCGAGCTCCACGTG	38 nM	(Kwon et al., 2015)
Iprobenfos	CGTACGGAATTCGCTAGCTAAGGGATTCCTGTAGAAGGAGCAGTCTGGATCCGAGCTCCACGTG	1.67 μM	(Kwon et al., 2015)
Bromacil	TGTACCGTCTGAGCGATTCGTACTGTGGGCACCAATCGTACCCAATACTTGCGAATCAGCCAGTCAGTGTTAAGGAGTGC	9.6 ± 7.8 nM	(Williams et al., 2014b)

although enzyme-linked immunosorbent assay (B. Liu et al., 2018; C. Shi et al., 2015) and capillary electrophoresis (D.Q. Li et al., 2018, 2017) were also applied for the detection of pesticide residues, they can not achieve on-site tests. On this ground, new biosensors such as optical biosensors and electrochemical biosensors, etc. were developed for the detection of pesticide residues, which are comparatively more convenient and sophisticated than traditional methods and can achieve field tests with rapid, specific and highly-sensitive detection.

Aptamers are short single-stranded oligonucleotides (RNA or DNA) developed through Systematic Evolution of Ligands by Exponential enrichment (SELEX) method, which can selectively bind to their targets with high affinity (Darmostuk et al., 2015; Z.X. Huang et al., 2017; M. Liu et al., 2018; M. Liu et al., 2017; Meng et al., 2016; Yang et al., 2011). Aptamers have several advantages over antibodies such as high-specificity, low molecular weight, a wide range of targets, easily synthesis and modification (Cansiz et al., 2015; K. Chen et al., 2017; R.R. Huang et al., 2017; M. Liu et al., 2018b; Meng et al., 2015; Xi et al., 2014, 2015), making them an ideal alternative for developing biosensors for the detection of pesticide residues. In addition, coupling with the fast development of nanotechnology and analyst methods, there have been large amounts of optical aptasensors and electrochemical aptasensors specifically developed for the detection of pesticide residues (Kim et al., 2016; Rapini and Marrazza, 2017; Zhou et al., 2014). Compared with antibody-based immunosensors and enzyme-based general biosensors for the detection of pesticide residues, aptasnsors exhibited better specificity and sensitivity, higher stability, more flexiblity, easier artificial synthesis, smarter as well as longer shelf life (Bagheri et al., 2018; Kim et al., 2016; Razmi et al., 2018). Moreover, the production of specific monoclonal antibodies utilized for immunosensors is tedious, very expensive and challenging, and there are batch-to-batch variations, which further limited their applications (Toh et al., 2015). In this short review, current aptamers specifically bind to various pesticides were first presented. Then, the development of various aptasensors for highly-sensitive and selective detection of pesticide residues were systematically reviewed. Finally, the present challenges and future perspectives for developing novel highly-effective aptasensor for pesticide residue detection were discussed.

2. Aptamers selected against pesticides

Over the past decades, the widely utilization of pesticides has caused lots of serious problems in the fields of both food safety and environment contamination. Therefore, large numbers of scientists are trying their best to develop rapid, sensitive and highly-specific methods for the detection of pesticide residues to effectively manage pesticide contamination and protect human beings. Under this circumstance, novel aptamers have attracted the attention of the researchers because of their well-known superiorities. To develop highly-effective aptamer-based biosensors (also known as aptasensors) for the detection of pesticide residues, pesticide-specific aptamer selection is inevitable and essential, which is the key factor for the development of aptasensors. Therefore, there have been a large number of researches focused on pesticides-specific aptamer selection. For example, a carbendazim-specific DNA aptamer was screened by Eissa and Zourob for the establishment of an electrochemical aptasensor for the detection of carbendazim residues in spiked food matrixes. The aptasensor was then demonstrated to be highly sensitive and selective with a detection limit of 42.9 pM and a linear range of 52.3 pM to 52.3 nM (Eissa and Zourob, 2017). Most recently, a highly specific single-stranded DNA (ssDNA) aptamer that specifically binds to fipronil with a Kd of 48 ± 8 nM was developed by Hong et al. which was then applied to establish a proof-of-principle fluorescent detection assay for the detection of fipronil in river water samples. This fluorescence assay showed highly-sensitivity to fipronil and low cross binding activity on various environmentally relevant, structurally unrelated herbicides and pesticides, whose detection limit in river samples achieved as low as 105 nM (Hong and Sooter, 2018). In addition, other pesticide-specific aptamers such as fluoroacetamide (Cao et al., 2016), acetamiprid (He et al., 2011), organophosphorus pesticides (Wang et al., 2012), etc. were also selected and widely applied for the detection of correlated pesticide residues both in food and environment management. Table 1 displayed the currently available aptamers specifically for the detection of various pesticide residues.

3. Aptasensors for pesticide detection

Over the past years, there have been various aptasensors developed for the detction of pesticide residues, including electrochemical aptasensors, fluorescent aptasensors, colorimetric aptasensors, chemiluminescent aptasensors, Surface-enhanced Raman scattering (SERS) based aptasensors, and so on. In this part, those aptasensors were systematically presented, and their merits as well as drawbacks were

elaborated.

3.1. Electrochemical aptasensors

In the past two decades, electrochemical aptasensors have displayed great potential for pesticide detection due to their multiplexed analysis, fast response, highly sensitivity, specificity and low cost (Y. Liu et al., 2018a; Y. Liu et al., 2017; Y. Liu et al., 2016; Rapini and Marrazza, 2017). To design an electrochemical aptasensor, the immobilization steps and strategies of signal amplification and assay approaches are three key processes. The most commonly used immobilization methods in developing electrochemical aptasensors include covalent bond formation, affinity reactions and self-assembled strategies (Y. Chen et al., 2017; Goud et al., 2016; Qin et al., 2016). Besides, for achieving high sensitivity, signal amplification is of the essence, and thus various strategies such as hybridization chain reaction (Ding et al., 2018; X.Y. Li et al., 2018), rolling circle amplification (Fan et al., 2018a; Li et al., 2016b), circular strand replacement DNA polymerization, target-triggered amplification (M. Chen et al., 2017), catalysis amplification (Y.Y. Wu et al., 2018; Yu et al., 2018; Zhao et al., 2017), and nanomaterial based amplification (Li et al., 2018a, 2018b), etc. were attempted to amplify the electrochemical signal during detection. In addition, based on the assay approaches, electrochemical aptasensors can be classified into label-free aptasensors and labeled aptasensors, which employed electrochemical impedance spectroscopy (EIS), sandwich and competitive strategies, respectively (He, 2018; Jiang et al., 2015; Prabhakar et al., 2016; Rapini and Marrazza, 2017; Yang et al., 2018; Zhang et al., 2017; Zhu et al., 2018). Herein, strategies for developing electrochemical aptasensors for pesticide detection were detailedly presented.

3.1.1. Label free electrochemical aptasensor

EIS is the most commonly employed approach for the development of label free electrochemical aptasensors, including Faradic EIS and non-Faradic EIS (Arya et al., 2018; Fan et al., 2013; Meini et al., 2012; Peng et al., 2009). Faradic EIS detection is based on the variation of the charge transfer resistance between the solution and the electrode surface, and requires the addition of redox-active species, such as $[Fe(CN)_6]^{3-/4-}$ or $[Ru(NH_3)_6]^{2+/3+}$ (Arya et al., 2018; Le et al., 2015; Madianos et al., 2018a; Meini et al., 2012). Whereas non-Faradic detection requires no additional reagents (Huy et al., 2011; Le et al., 2015). As a paradigm, Fei et al. (2015) developed an ultrasensitive label-free Faradic electrochemical impedimetric aptasensor for the detection of acetamiprid residues at femtomole level using gold nanoparticles (Au NPs) decorated multiwalled carbon nanotube-reduced graphene oxide nanoribbon (Au/MWCNT-rGONR) composites, which was based on that the variation of electron transfer resistance was relevant to the formation of acetamiprid–aptamer complex at the modified electrode surface (Fig. 1). The proposed Faradic electrochemical impedimetric aptasensor exhibited improved performance for the acetamiprid detection with simple operation processes, low-cost, high selectivity and sensitivity, a wide linear range of 50 fM to 10 μM, and an extremely low detection limit of 17 fM (Fei et al., 2015). In another experiment, Madianos et al. (2018a) developed a label free Faradic EIS based aptasensor utilizing two dimensional platinum nanoparticle (Pt NPs) films and target specific aptamers for highly selective detection of atrazine and acetamiprid simultaneously. Compared with conventional impedimetric sensors utilizing bare or “naked” interdigitated electrodes (IDEs), this aptasensor exhibited remarkably improved performance and can achieve simultaneous detection of acetamiprid and atrazine with a detection limit of 6 pM and 40 pM, respectively. To further improve the sensitivity and achieve a lower detection limit of the Faradic EIS based aptasenor, they incorporated platinum nanoparticle microwires and nanowires as the conductive material “bridging” the IDEs (Madianos et al., 2018b). Firstly, Pt NPs were deposited in a bridge-like arrangement between IDEs by employing the sputtering and e-beam lithography techniques to form Pt NP microwires. Then, the Pt NP microwires were chemically functionalized and covalently immobilized with aptamers against acetamiprid and atrazine on the biosensor surfaces (Fig. 2). When acetamiprid and atrazine bound to the immobilized aptamers, the electron transfer between the microwire-bridged IDEs would be inhibited and caused an increase in electrochemical impedance, allowing highly-sensitive detection. This improved Faradic EIS based aptasensor displayed higher sensitivity and selectivity in the detection of acetamiprid and atrazine residues in real samples. In the case of acetamiprid detection, the linear range was from 10 pM to 100 nM and the detection limit was as low as 1 pM, while in the case of atrazine detection, the linear range was from 100 pM to 1 μM and the detection limit was decreased to 10 pM

3.1.2. Labeled electrochemical aptasensor

Enzymes are among the most commonly utilized labels for the development of labeled electrochemical aptasensors, due to their catalytic ability to produce enzymatic products, which thereafter can be directly detected as electroactive species or can modify surface conductivity (Balamurugan et al., 2018; Danesh et al., 2016; Lei et al., 2018; Liu and Wei, 2014; Rapini and Marrazza, 2017; Wei and Feng, 2017; Yan et al., 2016). For example, Rapini et al. (2016) developed an innovative and simple electrochemical DNA aptasensor for sensitive multidetection of acetamiprid based on a competitive format and disposable screen-printed arrays. They progressively electrodeposited polyaniline film and gold nanoparticles on the graphite screen-printed electrode surface by cyclic voltammetry, and then modified the gold-polyaniline nano-

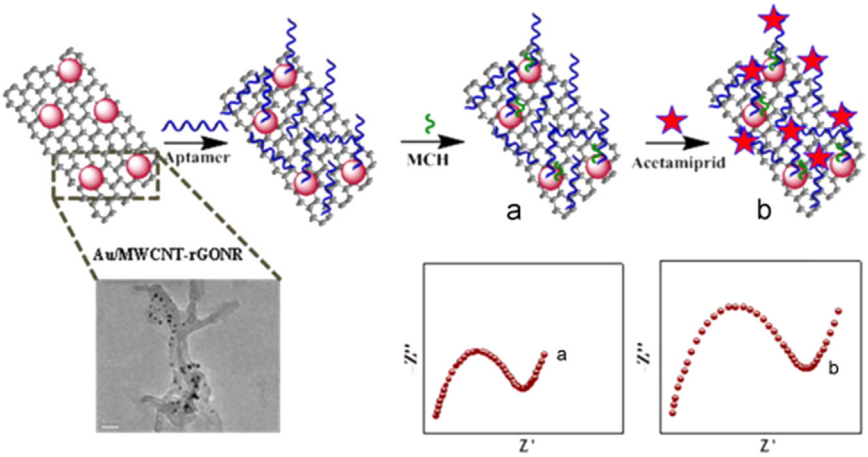

Fig. 1. Schematic representation of the impedimetric aptasensor fabrication and principle for acetamiprid determination. (Reproduced with permission from (Fei et al., 2015) Copyright 2015 Elsevier).

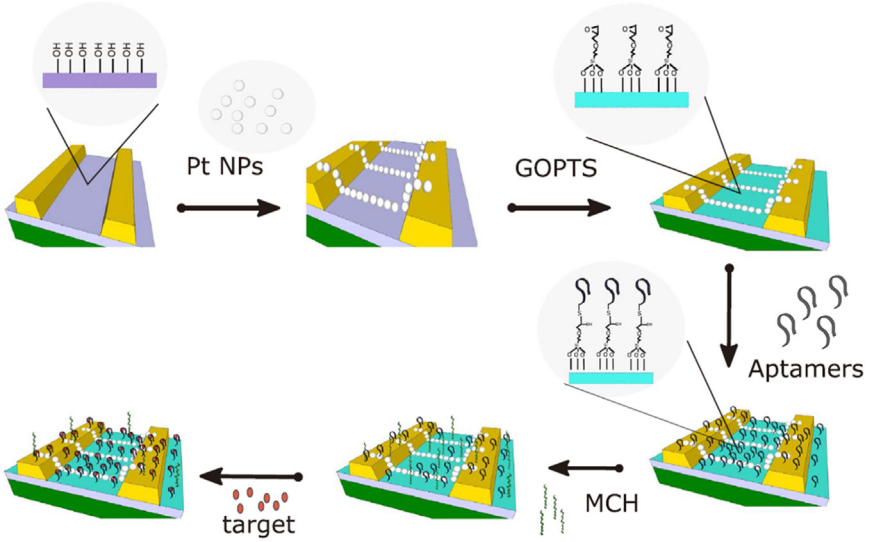

Fig. 2. Schematic illustration of the fabrication of the aptasensor. Following fabrication of the Pt NP microwires, the surfaces are silanized with (3-glycidyloxypropyl) triethoxysilane. Thiol-modified aptamers are covalently immobilized onto the surfaces and non-specifically bound aptamers are removed following incubation with 6-Mercapto-1-hexanol. (Reproduced with permission from (Madianos et al., 2018b) Copyright 2018 Elsevier).

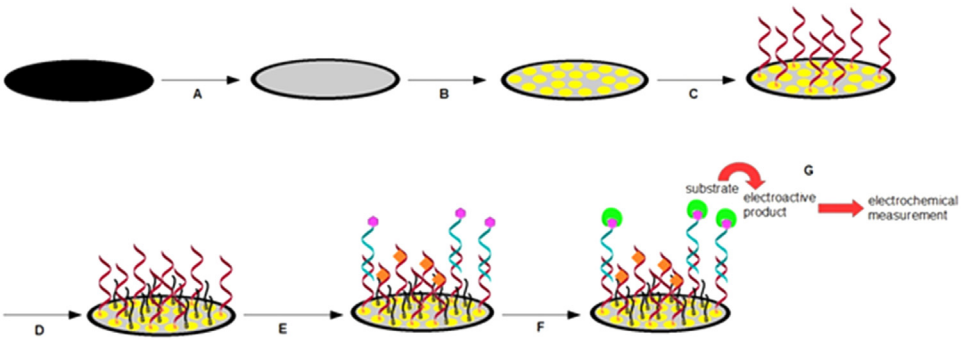

Fig. 3. Schematic illustration of the aptasensor assay for acetamiprid detection. A) electropolymerization of aniline; B) electrodeposition of gold nanoparticles (AuNPs); C) oligo1immobilization; D) mixed self-assembled monolayer formation with 6-mercapto-1-hexanol; E) competitive reaction between acetamiprid and complementary sequence (oligo2); F) coupling with streptavidin-alkaline phosphatase enzyme conjugate; G) incubation with 1-naphtyl phosphate and electrochemical detection of enzymatic product by DPV. (Reproduced with permission from (Rapini et al., 2016) Copyright 2016 Elsevier).

composite screen-printed electrodes with a mixed monolayer of a thiolated DNA aptamer and a spacer thiol, 6-mercapto-1-hexanol. For detection, different acetamiprid solutions containing a fixed amount of biotinylated complementary oligonucleotide sequence were interacted with the DNA aptasensor arrays, which were then incubated with streptavidin-alkaline phosphatase conjugate for signal amplification and followed catalysis of the hydrolysis of 1-naphthyl-phosphate to1-naphthol. Finally, the electroactive enzymatic product 1-naphthol was detected by Differential Pulse Voltammetry (DPV) (Fig. 3). The sensitivity, reproducibility and selectivity of the aptasensor were then studied using acetamiprid buffered solutions, and the detection limit reached 0.086 μM. In comparison with recently developed electrochemical aptasensors for acetamiprid multi-detection, this aptasensor is simpler, more portable and easier-to-prepare and thus is particularly promising for the realization of a commercial kit for acetamiprid residue detection (Rapini et al., 2016).

3.2. Fluorescent aptasensor

Fluorescence analysis is one of the most commonly sensing candidates for analysis of biomolecular interaction due to its particular advantages such as high sensitivity, high efficiency, simplicity and rapid analysis (Feng et al., 2014; Huang et al., 2016; Verdian, 2018; Wang et al., 2018b). Recently, benefited by the boom development of aptamers, various types of fluorescent aptasensors were developed for pesticide detection. Generally, there are two sensing strategies in developing fluorescent aptasensors, i.e., “signal-on” and “signal-off” sensing strategies, which typically employ the principle of fluorescence resonance energy transfer (FRET) (Bahreyni et al., 2018; Hu et al., 2016; Musumeci et al., 2017; Zhang et al., 2014). The change of fluorescence intensity is depended on the target binding, which allows for quantitative detection of pesticides. Coupling with the advantagies of nanomaterials, a number of nanomaterials such as quantum dots (QDs), carbon dots (CDs), up-conversion nanoparticles (UCNPs), Au NPs, Graphene oxide (GO), single-walled carbon nanotubes (SWNTs) and so on, have been synthesized and applied for developing various fluorescent aptasensors for the detection of pesticide residues (Abnous et al., 2016; Arvand and Mirroshandel, 2017; Bahreyni et al., 2018; Bala et al., 2018b; Dou et al., 2015; Guo et al., 2016; Wang et al., 2018a). Those aptasensors can achieve highly sensitive and rapid detection of pesticides without complex sample preparation. Here in this section, current progresses of developing fluorescent aptasensors for the detection of various pesticide residues were discussed in detail.

3.2.1. Fluorescent aptasensors based on “signal-on” strategy

The work mechanism of “signal-on” fluorescent aptasensors was characterized by the recovery or dramatically increased fluorescence intensity in the presence of target, whereas the fluorescence was quenched or negligible weak in the absence of the target. QDs, UCNPs and CDs are among the most employed nanomaterial-based fluorescers in fluorescent aptasensor system. For example, Lin et al., (Lin et al., 2016) constructed a novel “signal-on” aptasensor for quantification and imaging of acetamiprid. They coupled ZnS: Mn QDs with acetamiprid binding aptamer to obtain a fluorescence probe, whose fluorescence was quenched by multi-walled carbon nanotubes (MWCNTs) based on the FRET between ZnS: Mn-Aptamer and MWCNTs. When the acetamiprid was introduced, the ZnS: Mn-Aptamer would specifically bind to the acetamiprid, making the fluorescence recovered. The established aptasensor was remarkable sensitive and selective, and was very simple without complex operation. The linear range of the aptasensor was

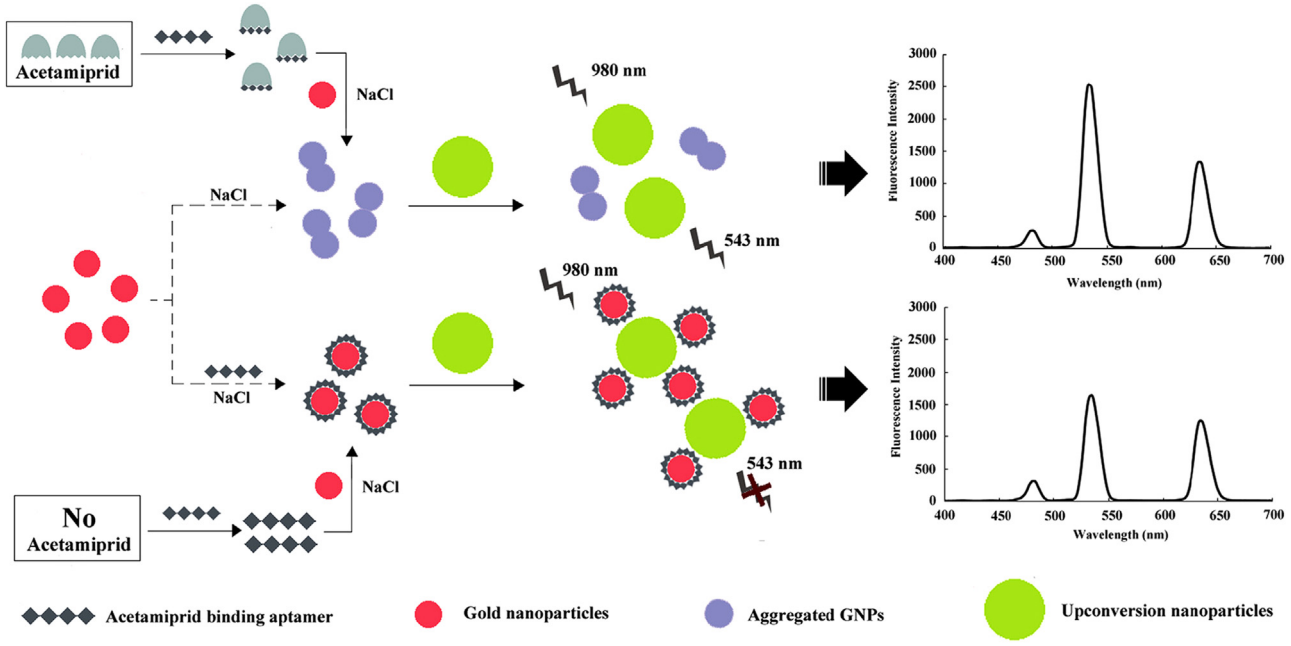

Fig. 4. Schematic representation of the UCNPs–Au NPs fluorescent aptasensor for the detection of acetamiprid. (Reproduced with permission from (Hu et al., 2016) Copyright 2016 Elsevier).

from 0 to 150 nM and the detection limit was as low as 0.7 nM (Lin et al., 2016). In another study, Hu and his coworkers developed a novel fluorescent nano-aptasensor for the detection of acetamiprid residues based on FRET between NH_2-$NaYF_4$: Yb, Ho@SiO_2 (UCNPs) and Au NPs (Fig. 4) (Hu et al., 2016). In this aptasensor, Au NPs served as the acceptors of FRET to efficiently quench the fluorescence of UCNPs. When acetamiprid in the samples specifically recognized and bound to the acetamiprid binding aptamer (ABA), the conformation of ABA would change from random coil to hairpin structure and caused varying aggregation extent of Au NPs in salt solution. Thus, the fluorescence of UCNPs was proportionally recovered, which depended on the acetamiprid concentration in the samples. After optimization, the efficiency of the fluorescent aptasensor for the acetamiprid detection was significantly enhanced with a linear concentration range from 50 nM to1 μM and a relatively low detection limit of 3.2 nM. Most recently, fluorescent CDs were also applied for the development of fluorescent aptasensor for pesticide detection. As a paradigm, Wang and his coworkers reported a novel fluorescent aptasensor for the detection of acetamiprid pesticide with high sensitivity and selectivity based on the inner filter effect (IFE) of AuNPs toward fluorescent CDs (Wang et al., 2018a). In this fluorescent aptasensor system, S-18 aptamer was employed as the specific target recognition ligand and free S-18 aptamer wraped AuNPs were utilized as the quenchers of fluorescent CDs through the IFE. In the presence of acetamiprid pesticide, the free S-18 aptamer sequences were exhausted by binding to the acetamiprid and thus caused aggregation of AuNPs, whose absorption spectrum no longer overlaped with the fluorescence emission spectrum of the CDs and led to obvious fluorescence recovery of the aptasensor. The proposed aptasensor displayed high selectivity and excellent accuracy for acetamiprid detection with a linear range from 22.5 nM to 0.45 μM and a detection limit of 4.85 nM.

Except for nanomaterials as fluorescers, there are a large number of nanomaterial-based quenchers applied in aptamsensor platforms for pesticide detection. Au NPs and GO are among the widest applied nanomaterial-based quenchers for establishing fluorescent aptasensors, due to their magnitude higher quenching effect than those of other organic quenching molecules (Emrani et al., 2016; Jiang et al., 2018; J.Y. Shi et al., 2015; Y. Shi et al., 2013). Besides, those Au NP- or GO-based fluorescent aptasensor can be easily engineered and can achieve multiplex detection without sophisticated design, due to their physical and chemical properties (Jiang et al., 2018; Kim et al., 2016; Song et al., 2009). For instance, Bahreyni et al., (Bahreyni et al., 2018) developed a fluorometric aptasensor using an aptamer against acetamiprid, multiple complementary strands (CSs), and AuNPs for the determination of neonicotinoid insecticide acetamiprid. In the absence of acetamiprid, the FAM-labeled CS2 would bind to AuNPs directly and indirectly through hybridization with CS3 immobilized on the surface of the AuNPs, making the fluorescence intensity be significantly quenched by the AuNPs. Whereas in the presence of acetamiprid, the acetamiprid would specifically bind to the aptamer and form CS1-fluorescein (FAM)-labeled CS2. Thus, the FAM-labeled dsDNA kept far away from the AuNPs and the fluorescence was recovered. The aptasensor can achieve ultrasensitive and selective detection of acetamiprid with a linear range of 5–50 nM and a detection limit of 2.8 nM. In another study, Cheng et al. (2018) developed a fluorescent aptamer-based lateral flow biosensor (apta-LFB) integrated with fluorophore-quencher nano-pairs and a smartphone spectrum reader for on-site detection of chlorpyrifos, diazinon, and malathion simultaneously. In this system, aptamers were utilized to alternatively recognize elements in LFB, while the novel fluorophore-quencher nano-pair (QDs and gold nanostars) was implemented to perform sensitive “signal-on” detection. After systematically optimization, the detection limits for the detection of chlorpyrifos, diazinon, and malathion were determined to be about 2.08 nM, 22.01 nM, and 2.24 nM, respectively, which was very promising for practical on-site application of multi-pesticide detection (Cheng et al., 2018). Furthermore, taking the advantages of excellent optical properties and biocompatibility of single-strand DNA-functionalized QDs, Arvand and Mirroshandel developed an aptasensor by immobilizing the aptamer on water soluble L-cysteine capped ZnS QDs for the determination of edifenphos (EDI) in real samples (Arvand and Mirroshandel, 2017). In this aptasensor system, aptamer-conjugated QDs were bound to the GO sheets to form a GO/aptamer-QDs ensemble, causing quenching the fluorescence of QDs through FRET from the QDs to the GO sheets. When the aptamer bound to the EDI, the GO was replaced and the fluorescence of QDs was restored. The fluorescence intensity was proportional to the EDI concentration, making the aptasensor capable of quantitative detection. Under the optimum conditions, the GO-based aptasensor exhibited excellent analytical

performance for highly sensitive and selective determination of EDI with a linear range from 1.61 nM to 19.33 nM and a detection limit of 0.42 nM.

3.2.2. Fluorescent aptasensors based on "signal-off" strategy

The work mechanism of "signal-off" fluorescent aptasensors was characterized by the quencher or dramatically increased fluorescence intensity in the presence of target, whereas the fluorescence was strong in the absence of the target. For instance, X. Liu et al. (2016) developed an aptamer-based fluorescent sensing platform using triple-helix molecular switch (THMS) for the pesticide screening represented by acetamiprid. There were two tailored DNA probes in the THMS, which are a label-free central target specific aptamer sequence flanked by two arm segments acting as a recognition probe and a hairpin-shaped structure oligonucleotide serving as a signal transduction probe (STP). The STP was labeled with a fluorophore and a quencher at the 3′ and 5′-end, respectively. In the absence of acetamiprid, the two arm segments of the aptamers would bind with the loop sequence of STP via hybridization and enforce the formation of "open" configuration of STP, and turn on the fluorescence of THMS. While in the presence of target acetamiprid, the aptamer-acetamiprid binding would disassemble the THMS and release the STP. The free STP then folded into a stem loop structure, causing fluorescence quenching. The quenched fluorescence intensity was proportional to the concentration of acetamiprid in the range from 0.1 to 1.2 μM, with a detection limit of 9.12 nM (X. Liu et al., 2016). In addition, Bala et al. (2018b) synthesized a novel CdTe@CdS QD-based nanoprobe using guanidinium-containing polymer, namely poly(N-(3-guanidinopropyl)methacrylamide) homopolymer (PGPMA) as a quencher and an aptamer as a recognition element for the highly sensitive detection of malathion. In this detection platform, the interaction of the aptamer with malathion would switch off the fluorescence signal of the probe, resulting in the quenching of the QDs. While there was no malathion in the samples, the polymer would interact with the aptamer via electrostatic interactions and thereby recover the fluorescence of QDs unaffected (Fig. 5). The detection platform was then demonstrated to exhibit excellent sensitivity towards malathion with a wide linear range from 10 pM to 1 μM and a detection limit of 4 pM (Bala et al., 2018b).

3.3. Colorimetric aptasensor

Colorimetric methods have been extensively applied for the detection of pesticide contaminants in food and environment because of their excellent merits including easy preparation, lower cost, and clear observation of the results with naked eyes (L.Y. Lan et al., 2017; Y. Liu et al., 2018b; H. Shi et al., 2013; Song et al., 2011; Yue et al., 2016). Au NPs and silver nanoparticles (Ag NPs) are among the most commonly used probes for colorimetric sensing assays due to their simple preparation and surface modification, as well as surface plasmon resonance properties that assist the detection assay in producing a colorimetric signal (Bala et al., 2016a, 2016b; Jokar et al., 2016; Priyadarshini and Pradhan, 2017). For example, Wang et al. (2015) developed a simple and selective aptamer-based colorimetric assay for the detection of omethoate based on the resistance of ssDNA-wrapped Au NPs to salt-induced aggregation. In this aptasensor, omethoate-binding aptamers were wrapped on the surface of Au NPs to fabricate aptamer-wrapped Au NPs. In the presence of omethoate, aptamers would specifically bind to omethoate and disconnected from Au NPs, resulting in Au NPs aggregation and color changes. The established aptasensor showed good linearity between 0.1 and 10 μM, with a low detection limit of 0.1 μM. Similarly, taking advantages of a hairpin structure consisting of a complementary strand of aptamer and a double-stranded DNA (dsDNA) structure to protect Au NPs against salt-induced aggregation, Abnous et al. (2018) developed a method for the colorimetric determination of pesticide malathion (Fig. 6). In the absence of malathion, the dsDNA structure on the surface of Au NPs protected Au NPs from aggregation in solutions containing NaCl. While, in the presence of malathion, the aptamer turned into a hairpin structure to form aptamer/malathion complex and the complementary strands were released to the solution. As a result, the Au NPs underwent salt-induced aggregation, making the solution color change from red to blue. Thereafter, the method was successfully applied to the determination of malathion in spiked human serum samples, which was able to quantify malathion within 35 min with a linear range from 5 pM to 10 nM and a detection limit of 1 pM (Abnous et al., 2018).

Similar to Au NPs, Ag NPs can also exhibited color change in solution and thus being applied for colorimetric detection of pesticides. As a paradigm, employing a basic hexapeptide KKKRRR, a malathion specific aptamer and Ag NPs as a nanoprobe, Bala et al. (2018a) engineered a supersensitive Ag NPs based aptasensor for low cost detection of malathion residues in various water and apple samples (Fig. 7). The solution would keep yellow in the absence of malathion due to the binding of aptamer with peptide, whereas it would change to orange in the presence of malathion owing to the agglomeration of Ag NPs. The developed aptasensor exhibited excellent selectivity against malathion with a very low detection limit of 0.5 pM and high recovery range of 89–120%, which is very promising for highly selective and sensitive colorimetric sensing of trace levels of malathion in complex samples.

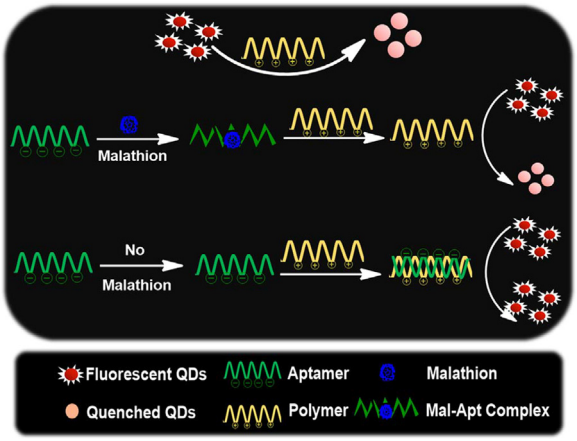

Fig. 5. Schematic representation of the principle for the detection of malathion. The fluorescence of the QDs is quenched in the presence malathion due to the availability of the polymer while in the absence of malathion, polymer is bound to the aptamer thereby preventing the quenching of QDs. (Reproduced with permission from (Bala et al., 2018b) Copyright 2018 Elsevier).

3.4. Chemiluminescent aptasensor

Chemiluminescent method, a phenomenon of light emission based on multistep oxidation reactions, is another commonly applied method for the detection of pesticides (He et al., 2018; Ouyang et al., 2018). Compared with fluorescent and electrochemical methods, chmeiluminescent method has several advantages such as wide dynamic range, high signal-to-noise ratio, high sensitivity, simple operation and no need of expensive excitation source and specialized filter (Ali et al., 2017; Liu et al., 2015; Tang et al., 2013; Wang et al., 2016; Xi et al., 2015; Zhou et al., 2016). For instance, taking advantages of the specific binding ability of aptamers to targets and catalytic effect of AuNPs to stimulate the generation of chemiluminescence signal in the presence of H_2O_2 and luminol, Qi et al. (2016) developed an amplified chemiluminescence aptasensor for ultrasensitive and selective acetamiprid detection. In this detection system, morphology change (from dispersed state to aggregated state) of AuNPs caused by acetamiprid-induced conformational change of aptamers could be sensitively differentiated by chemiluminescence signal produced by the AuNPs (Fig. 8). The proposed aptasensor was then demonstrated to be highly sensitive to

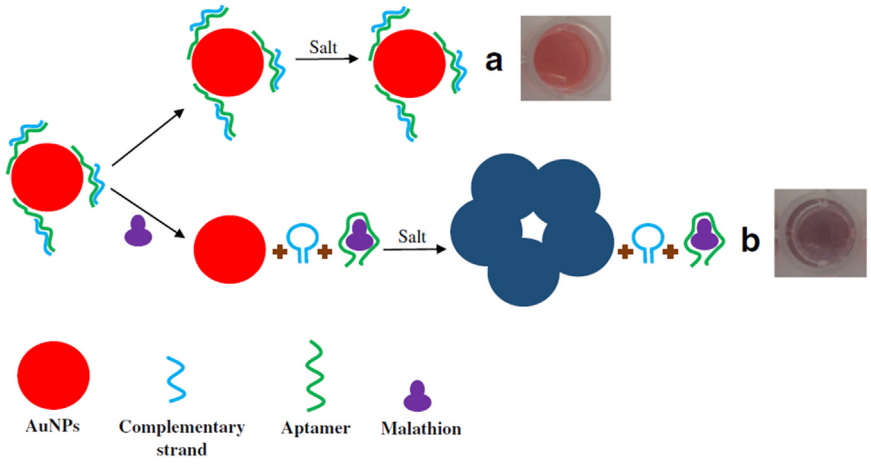

Fig. 6. Schematic representation of the malathion detection based on dsDNA modified AuNPs and hairpin structure of complementary strand. (Reproduced with permission from (Abnous et al., 2018) Copyright 2018 Springer Nature).

acetamiprid with a detection limit of 62 pM, which was about 100-fold lower than that of other aptamer-based sensors for acetamiprid detection, providing a label-free and cost-effective approach for sensitive detection of single component acetamiprid residues (Qi et al., 2016). Moreover, Li et al. (2016a) constructed an electrogenerated chemiluminescence (ECL) sensing platform for carbofuran detection based on ECL energy transfer and carbon dot (C-dot)-tagged aptamers as the recognition element. The aptasensor exhibited high sensitivity towards carbofuran with a linear ECL response to carbofuran ranging from 20 pM to 8.0 nM and a detection limit of 0.88 pM

3.5. Surface-enhanced Raman scattering based aptasensor

Surface-enhanced Raman scattering (SERS) is a powerful spectroscopic technique utilizing the surface-sensitive resonance extension of standard Raman spectroscopy that can achieve trace detection of interest molecules when excited in the vicinity of or on rough metal substrates with an increase in Raman scattering up to 10 orders of magnitude (Gillibert et al., 2018; Muehlethaler et al., 2016; Pieczonka and Aroca, 2008; Vendrell et al., 2013). Compared with other analytical methods, SERS exhibits several advantages such as high sensitivity, excellent multiplexing capabilities, minimal photobleaching, and low background from water (Li et al., 2014; Nie et al., 2018; Vendrell et al., 2013; Yan et al., 2018). And thus, coupling with the high specificity and binding affinity of aptamers, the development of SERS based aptasensors for the trace detection of pesticide residues has attracted attention. For example, taking advantages of the ability of thiolated aptamer conjugated silver dendrites to enhance the Raman fingerprint of pesticides, through silver–thiol bonds, Pang et al. (2014) develop a simple and rapid SERS-based aptasensor for simultaneously detection and discrimination among isocarbophos, omethoate, phorate, and profenofos. Particularly, thiolated aptamers were conjugated onto silver dendrites through silver–thiol bonds followed by backfilling with 6-mercaptohexanol to prevent nonspecific binding. Upon detection, the modified SERS platform was mixed with each pesticide solution for 20 min and analyzed under a DXR Raman microscope and TQ Analyst software. These results demonstrated that the established aptasensor was able to detect and discriminate isocarbophos, omethoate, phorate, and profenofos with detection limits of 3.4 mM (1 ppm), 24 mM (5 ppm), 0.4 mM (0.1 ppm), and 14 mM (5 ppm) respectively (Pang et al., 2014). Moreover, Nie et al. (2018) developed a novel label-free SERS based aptasensor for trace detection of malathion residues (Fig. 9). In this sensing platform, the silver nanoparticles were first modified with positively charged spermine to enhance the capture of the negatively charged aptamer. Then, the silver nanoparticle-aptamer complexes were used to specifically capture the malathion, followed by SERS spectrum recording. Finally, the selectivity and sensitivity of this aptasensor were verified and elucidated by using the mixed-pesticide

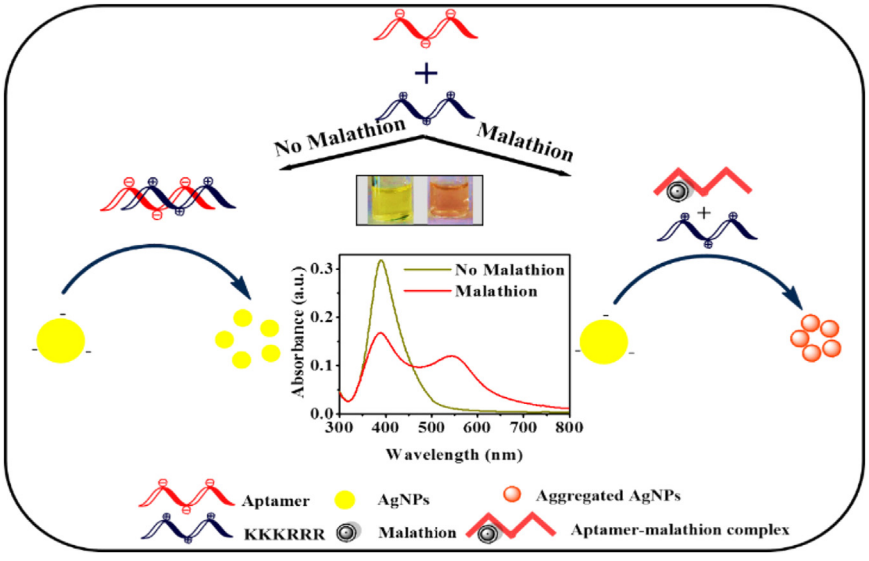

Fig. 7. Schematic illustration of the aptasensor for malathion detection by employing Ag NPs. The color of the sample remains yellow in the absence of malathion owing to the binding of aptamer with peptide KKKRRR, whereas the color changes to orange in the presence of malathion due to the specific binding of aptamer to malathion and thereby rendering KKKRRR free to aggregate Ag NPs. (Reproduced with permission from (Bala et al., 2018a) Copyright 2018 Elsevier).

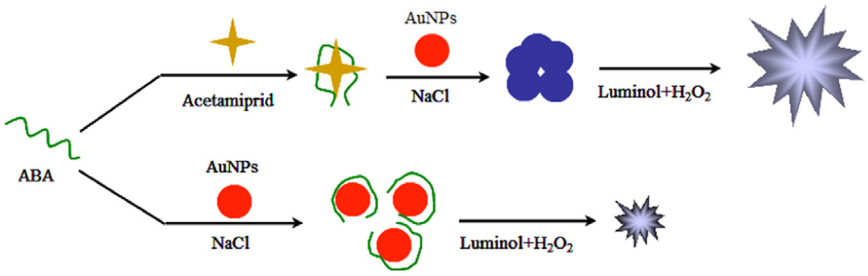

Fig. 8. Schematic illustration of the chemiluminescence aptasensor for acetamiprid detection. (Reproduced with permission from (Qi et al., 2016) Copyright 2016 Elsevier).

standard solution and the aggregate reagents (NaCl, KCl, $MgCl_2$), respectively. The proposed label-free SERS based aptasensor was convenient, and could achieve special detection of trace malathion residues with a good linear range of 500 nM to 10 μM and good recoveries from 87.4% to 110.5% with a relative standard deviation of less than 4.22% in spiked tap water.

3.6. Other aptasensors

Aptamers coupled with capillary electrophoresis (CE) (Tang et al., 2016) and microfluidic chip (S. Li et al., 2018) are also potential sensing methods for highly sensitive detection of pesticides. CE displayed great potential for pesticide analysis due to its advantages of high separation efficiency, high analysis speed, highly automated operation, and very small consumption of reagents (Lu et al., 2018; Tang et al., 2016). By integrating the advantages of specific binding ability of aptamers and high analysis speed of CE, the established CE-based aptasensor will dramatically accelerate the sensitivity, shorten detection time, and improve accuracy of trace pesticides detection. Microfluidic chip is a technique for manipulating microfluidic fluids in a micrometre-sized channel that is able to perform sample pre-treatment, separation, and detection in one assay (S. Li et al., 2018; Liao et al., 2018; Sackmann et al., 2014). Compared with the conventional methods for the detection of pesticide residues, microfluidic chip provided a more advanced and convenient technology for the determination of pesticide residues, owing to its advantages associated with miniaturization, improved sensitivity and specificity, ease of multiplexing and integration, high portability, versatility in design, fast and cheap way of analysis, and multiple and parallel sample detection (Kant et al., 2018; Kecskemeti and Gaspar, 2018; Liao et al., 2018). As a paradigm, Fujii et al. (2017) developed an aptamer-based microfluidic chip biosensor for omethoate vapor detection using a DNA aptamer, nanopore, and agarose gel. Particularly, a droplet interface bilayer was first developed by a droplet contact method (Fig. 10a). Then, an agarose gel was used to replace one of the aqueous droplets-in-oil to act as an absorbent of omethoate vapor (Fig. 10b). Finally, a DNA aptamer specifically bind to omethoate was introduced for its sensitive detection (Fig. 10c). In the presence of the target, the DNA aptamer would transform its structure and form a bulky complex with omethoate, which clogged at the nanopore and provided a signal of a long blocked current (Fig. 10d and e). The established aptasensor exhibited high specificity and sensitivity to omethoate with a detection limit of 4.8 nM in solution and 100 ppb as vapor, and a detection time of about 60 s (Fujii et al., 2017).

4. Conclusions and future perspectives

In the past decades, the wide application of pesticides in agriculture industry has caused serious pesticide residues in food and environment, forming a severe public health problem to human beings. To achieve good management of this problem, highly-sensitive detection of pesticide residues is very important. However, the conventional detection methodologies cannot realize highly sensitive, selective and on-site detection, which limits their applications. Therefore, benefited from the booming development of aptamers and their obvious superiorities, development of various aptasensors for fast, selective, sensitive and on-site detection of pesticide residues has attracted much attention. In this short review, aptamers specifically bind to various pesticides were first summarized. Then the current progress of developing aptasensors for highly-sensitive and selective detection of pesticide residues were systematically discussed, including electrochemical aptasensors, fluorescent aptasensors, colorimetric aptasensors, chemiluminescent aptasensors, SERS based aptasensors, and so on. The performance of those aptasensors is briefly shown in Table 2, which shows great potential in the management of the public health problem caused by pesticide residues.

Although these aptasensors play very well in controlling pesticide contamination and have achieved some success, there are still many challenges needing to be addressed. Firstly, from the viewpoint of aptasensor development, each aptasensor type has its advantages and shortcomings. Electrochemical aptasensors can achieve multiplexed analysis and on-site detection with fast response, highly sensitivity and specificity, low cost and simple operation. However, the stability of electrochemical aptasensors should be improved and the strict pretreatments of samples are always required (Huang et al., 2018; Jalalian

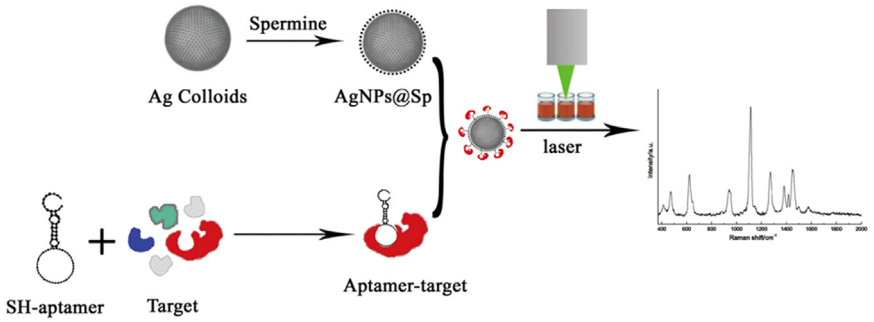

Fig. 9. Schematic illustration of the label-free SERS based aptasensor for the detection of malathion residues. (Reproduced with permission from (Nie et al., 2018) Copyright 2018 Elsevier).

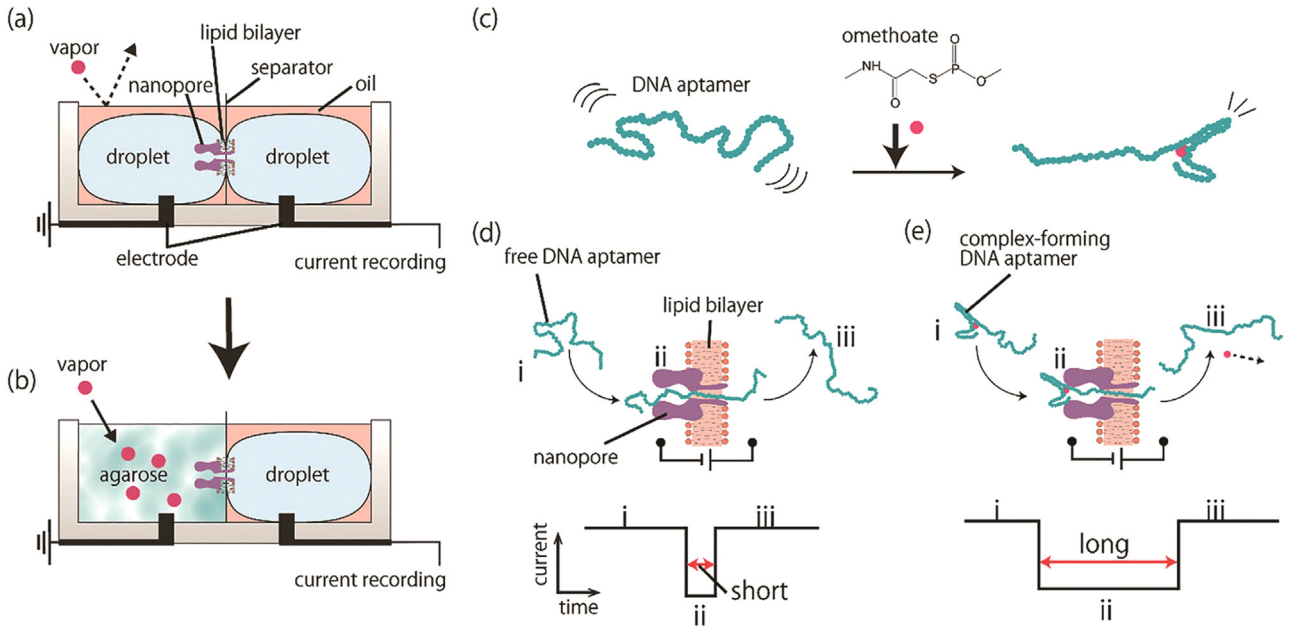

Fig. 10. Schematic illustration of the aptamer-based microfluidic chip biosensor for omethoate vapor detection using a DNA aptamer, nanopore, and agarose gel. (Reproduced with permission from (Fujii et al., 2017) Copyright 2017 Royal Society of Chemistry).

et al., 2018; Rapini and Marrazza, 2017; Vasilescu and Marty, 2016). Fluorescent aptasensors can also achieve high sensitive detection with high efficiency, simplicity and rapid analysis in various samples, but the fluorescence lifetime and fluorescence background can influence the stability and accurance of the aptasensors (Emrani et al., 2016; Li et al., 2015; Sergelen et al., 2017; Velu et al., 2015; Yellen and Mongeon, 2015). Moreover, colorimetric aptasensors can achieve clear observation of the results with naked eyes with simplicity, practicality and very low cost, while they can not achieve multiple detection and quantitative detection without the help of other instruments, and the sensitivity needs to be further increased (Sabela et al., 2017; Yazdian-Robati et al., 2018). Chemiluminescent aptasensors show preferable sensitivity, low detection limits, wide linear ranges, and good speed of response, but the processes are complex and need enzymes and special instruments (Sharma et al., 2015; Sun and Lu, 2018). In addition, although SERS can achieve trace detection of interest molecules, the SERS based aptasensor still displayed high detection limit and bad reproducibility, which remains to be improved in the future (Shi et al., 2017). Finally, microfluidic chip shows many advantages over the above methods, such as ease of multiplexing and integration, high portability, versatility in design, fast and cheap way of analysis, and multiple and parallel sample detection, but the detection throughput is some low and the requirements for sample pretreatment are high and strict (Y.Y. Fan et al., 2018; Liao et al., 2018). Therefore, how to integrate the superiorities and avoid the drawbacks of those detection methods is an important task in the development of new aptasensors for the detection of

Table 2
Aptasensors for the detection of pesticide residues.

Method Type	Target	Sample	Linear range	Detection limit	Reference
electrochemical	acetamiprid	real water	50 fM to 10 μM	17 fM	Fei et al. (2015)
electrochemical	acetamiprid	real water	10 pM to 100 nM	1 pM	Madianos et al. (2018b)
electrochemical	acetamiprid	fruit juice		0.086 μM	Rapini et al. (2016)
electrochemical	atrazine	real water	100 pM to 1 μM	10 pM	Madianos et al. (2018b)
fluorescent	acetamiprid	river water and cabbage leaves	0–150 nM	0.7 nM	Lin et al. (2016)
fluorescent	acetamiprid	tea	50 nM to 1 μM	3.2 nM	Hu et al. (2016)
fluorescent	acetamiprid	tomatoes, cucumber and cabbage	22.5 nM to 0.45 μM	4.85 nM	Wang et al. (2018)
fluorescent	acetamiprid	tap water	5–50 nM	2.8 nM	Bahreyni et al. (2018)
fluorescent	chlorpyrifos	vegetable		2.08 nM	Cheng et al. (2018)
fluorescent	diazinon			22.01 nM	Cheng et al. (2018)
fluorescent	malathion			2.24 nM	Cheng et al. (2018)
fluorescent	edifenphos	water and rice	1.61–19.33 nM	0.42 nM	Arvand and Mirroshandel (2017)
fluorescent	acetamiprid	vegetable	0.1 μM to 1.2 μM	9.12 nM	X. Liu et al. (2016)
fluorescent	malathion	water, soil and orange juice	10 pM to 1 μM	4 pM	Bala et al. (2018b)
colorimetric	omethoate	soil	0.1 μM to 10 μM	0.1 μM	Wang et al. (2015)
colorimetric	malathion	human serum	5 pM to 10 nM	1 pM	Abnous et al. (2018)
colorimetric	malathion	apple		0.5 pM	Bala et al. (2018a)
chemiluminescent	acetamiprid	waste water, soil and cucumbers		62 pM	Qi et al. (2016)
chemiluminescent	carbofuran	fruit and vegetable	20 pM to 8.0 nM	0.88 pM	Li et al. (2016)
SERS	isocarbophos	apple juice		3.4 mM	Pang et al. (2014)
SERS	omethoate			24 mM	Pang et al. (2014)
SERS	phorate			0.4 mM	Pang et al. (2014)
SERS	profenofos			14 mM	Pang et al. (2014)
SERS	malathion	tap water	500 nM to 10 μM		Nie et al. (2018)
microfluidic chip	omethoate	vapor		4.8 nM	Fujii et al. (2017)

pesticide residues. Secondly, for the development of aptasensors, sufficient aptamers are essential. However, up to date, there are only several pesticide-specific aptamers developed and some of those aptamers lack selectivity, which is not able to distinguish among pesticide analogues. Thus, more highly pesticide-specific aptamers need to be selected by SELEX. Thirdly, the strategies for the development of aptasensors need to be updated and innovated to achieve better pesticide determination and on-site detection. To do this, new nanomaterials and high-efficient signal amplification methods are essential. Finally, there are still many challenges in the detection of real complex samples, due to the varieties of interfering substances. Therefore, how to improve the capacity of resisting disturbance of those aptasensors is very significant, providing a new chance for fabricating new smart aptasensors for the on-field detection of pesticide residues without complex and tedious sample pretreatment.

CRediT authorship contribution statement

Mei Liu: Writing - original draft. **Arshad Khan:** Writing - review & editing. **Zhifei Wang:** Writing - review & editing. **Yuan Liu:** Formal analysis. **Gaojian Yang:** Conceptualization. **Yan Deng:** Funding acquisition. **Nongyue He:** Supervision.

Acknowledgments

This work was supported by the NSF of China (61527806, 61471168 and 61871180), the National Key Research and Development Program of China (2017YFA0205301 and 2018YFC1602905) and Open Funding of State Key Laboratory of Oral Diseases (SKLOD2018OF02).

Conflicts of interest

The authors declare no conflicts of interest.

Declaration of interests

None.

References

Abnous, K., Danesh, N.M., Ramezani, M., Alibolandi, M., Emrani, A.S., Lavaee, P., Taghdisi, S.M., 2018. Microchim. Acta 185, 216 (UNSP).
Abnous, K., Danesh, N.M., Ramezani, M., Alibolandi, M., Lavaee, P., Taghdisi, S.M., 2016. Microchim. Acta 184, 81–90.
Ali, Z., Wang, J.H., Tang, Y.J., Liu, B., He, N.Y., Li, Z.Y., 2017. Biomater. Sci. 5, 57–66.
Arvand, M., Mirroshandel, A.A., 2017. Biosens. Bioelectron. 96, 324–331.
Arya, S.K., Zhurauski, P., Jolly, P., Batistuti, M.R., Mulato, M., Estrela, P., 2018. Biosens. Bioelectron. 102, 106–112.
Bagheri, E., Abnous, K., Alibolandi, M., Ramezani, M., Taghdisi, S.M., 2018. Biosens. Bioelectron. 111, 1–9.
Bahreyni, A., Yazdian-Robati, R., Ramezani, M., Abnous, K., Taghdisi, S.M., 2018. Microchim. Acta 185, 272.
Bala, R., Kumar, M., Bansal, K., Sharma, R.K., Wangoo, N., 2016a. Biosens. Bioelectron. 85, 445–449.
Bala, R., Mittal, S., Sharma, R.K., Wangoo, N., 2018a. Spectrochim. Acta A Mol. Biomol. Spectrosc. 196, 268–273.
Bala, R., Sharma, R.K., Wangoo, N., 2016b. Anal. Bioanal. Chem. 408, 333–338.
Bala, R., Swami, A., Tabujew, I., Peneva, K., Wangoo, N., Sharma, R.K., 2018b. Biosens. Bioelectron. 104, 45–49.
Balamurugan, M., Santharaman, P., Madasamy, T., Rajesh, S., Sethy, N.K., Bhargava, K., Kotamraju, S., Karunakaran, C., 2018. Biosens. Bioelectron. 116, 89–99.
Cansiz, S., Zhang, L.Q., Wu, C.C., Wu, Y., Teng, I.T., Hou, W.J., Wang, Y.Y., Wan, S.O., Cai, R., Jin, C., Liu, Q.L., Tan, W.H., 2015. Chem.-Asian J. 10, 2084–2094.
Cao, F., Lu, X., Hu, X., Zhang, Y., Zeng, L., Chen, L., Sun, M., 2016. Biosci. Biotechnol. Biochem. 80, 823–832.
Carvalho, F.P., 2017. Food Energy Secur. 6, 48–60.
Chen, K., Liu, B., Yu, B., Zhong, W., Lu, Y., Zhang, J.N., Liao, J., Liu, J., Pu, Y., Qiu, L.P., Zhang, L.Q., Liu, H.X., Tan, W.H., 2017a. Wires Nanomed. Nanobi 9, e1438 (UNSP).
Chen, M., Gan, N., Li, T.H., Wang, Y., Xu, Q., Chen, Y.J., 2017b. Anal. Chim. Acta 968, 30–39.
Chen, Y., Zhou, S.W., Li, L.L., Zhu, J.J., 2017c. Nano Today 12, 98–115.
Cheng, N., Song, Y., Fu, Q., Du, D., Luo, Y., Wang, Y., Xu, W., Lin, Y., 2018. Biosens. Bioelectron. 117, 75–83.
Christodoulou, D.L., Kourouzidou, O., Hadjigeorgiou, M., Hadjiloizou, P., Constantinou, M., Constantinou, P., Kika, K., Klavarioti, M., 2018. Accredit. Qual. Assur. 23, 145–175.
Danesh, N.M., Ramezani, M., Emrani, A.S., Abnous, K., Taghdisi, S.M., 2016. Biosens. Bioelectron. 75, 123–128.
Darmostuk, M., Rimpelova, S., Gbelcova, H., Ruml, T., 2015. Biotechnol. Adv. 33, 1141–1161.
Ding, S.H., Gu, Z.P., Yan, R.H., Tang, Y.G., Miao, P., 2018. Anal. Chim. Acta 1029, 24–29.
Dou, X.W., Chu, X.F., Kong, W.J., Luo, J.Y., Yang, M.H., 2015. Anal. Chim. Acta 891, 291–297.
Eddleston, M., Buckley, N.A., Eyer, P., Dawson, A.H., 2008. Lancet 371, 597–607.
Eissa, S., Zourob, M., 2017. Anal. Chem. 89, 3138–3145.
Emrani, A.S., Danesh, N.M., Lavaee, P., Ramezani, M., Abnous, K., Taghdisi, S.M., 2016. Food Chem. 190, 115–121.
Fan, L., Zhao, G., Shi, H., Liu, M., Li, Z., 2013. Biosens. Bioelectron. 43, 12–18.
Fan, T.T., Du, Y., Yao, Y., Wu, J., Meng, S., Luo, J.J., Zhang, X., Yang, D.Z., Wang, C.Y., Qian, Y., Gao, F.L., 2018a. Sens. Actuators B-Chem. 266, 9–18.
Fan, Y.Y., Dong, D.F., Li, Q.L., Si, H.B., Pei, H.M., Li, L., Tang, B., 2018b. Lab Chip 18, 1151–1173.
Fei, A., Liu, Q., Huan, J., Qian, J., Dong, X., Qiu, B., Mao, H., Wang, K., 2015. Biosens. Bioelectron. 70, 122–129.
Feng, C.J., Dai, S., Wang, L., 2014. Biosens. Bioelectron. 59, 64–74.
Fujii, S., Nobukawa, A., Osaki, T., Morimoto, Y., Kamiya, K., Misawa, N., Takeuchi, S., 2017. Lab Chip. 17, 2421–2425.
Gillibert, R., Huang, J.Q., Zhang, Y., Fu, W.L., de la Chapelle, M.L., 2018. Trac-Trend Anal. Chem. 105, 166–172.
Goud, K.Y., Catanante, G., Hayat, A., Satyanarayana, M., Gobi, K.V., Marty, J.L., 2016. Sens. Actuators B-Chem. 235, 466–473.
Guo, J., Li, Y., Wang, L., Xu, J., Huang, Y., Luo, Y., Shen, F., Sun, C., Meng, R., 2016. Anal. Bioanal. Chem. 408, 557–566.
He, B.S., 2018. Microchim. Acta 185, 344 (UNSP).
He, J., Liu, Y., Fan, M., Liu, X., 2011. J. Agr. Food Chem. 59, 1582–1586.
He, L., Jiang, Z.W., Li, W., Li, C.M., Huang, C.Z., Li, Y.F., 2018. ACS Appl. Mater. Interfaces 10, 28868–28876.
Hong, K.L., Sooter, L.J., 2018. Int. J. Mol. Sci. 19, 85.
Hu, W.W., Chen, Q.S., Li, H.H., Ouyang, Q., Zhao, J.W., 2016. Biosens. Bioelectron. 80, 398–404.
Huang, R.R., Chen, Z.S., Liu, M., Deng, Y., Li, S., He, N.Y., 2017a. Sci. China Chem. 60, 786–792.
Huang, R.R., He, N.Y., Li, Z.Y., 2018. Biosens. Bioelectron. 109, 27–34.
Huang, R.R., Xi, Z.J., Deng, Y., He, N.Y., 2016. Sci. Rep. 6, 31103.
Huang, Z.X., Xie, Q., Guo, Q.P., Wang, K.M., Meng, X.X., Yuan, B.Y., Wan, J., Chen, Y.Y., 2017b. Chin. Chem. Lett. 28, 1252–1257.
Huy, T.Q., Nguyen, T.H.H., Thuy, N.T., Van Chung, P., Nga, P.T., Tuan, M.A., 2011. Talanta 86, 271–277.
Jalalian, S.H., Karimabadi, N., Ramezani, M., Abnous, K., Taghdisi, S.M., 2018. Trends Food Sci. Technol. 73, 45–57.
Jiang, C.M., Lan, L.Y., Yao, Y., Zhao, F.N., Ping, J.F., 2018. Trac-Trends Anal. Chem. 102, 236–249.
Jiang, D., Du, X.J., Liu, Q., Zhou, L., Dai, L.M., Qian, J., Wang, K., 2015. Analyst 140, 6404–6411.
Jokar, M., Safaralizadeh, M.H., Hadizadeh, F., Rahmani, F., Kalani, M.R., 2016. J. Biomol. Struct. Dyn. 34, 2505–2517.
Kant, K., Shahbazi, M.A., Dave, V.P., Ngo, T.A., Chidambara, V.A., Than, L.Q., Bang, D.D., Wolff, A., 2018. Biotechnol. Adv. 36, 1003–1024.
Kecskemeti, A., Gaspar, A., 2018. Anal. Chim. Acta 1021, 1–19.
Kim, Y.S., Raston, N.H.A., Gu, M.B., 2016. Biosens. Bioelectron. 76, 2–19.
Kwon, Y.S., Nguyen, V.T., Park, J.G., Gu, M.B., 2015. Anal. Chim. Acta 868, 60–66.
Lan, L., Yao, Y., Ping, J., Ying, Y., 2017a. ACS Appl. Mater. Interfaces 9, 23287–23301.
Lan, L.Y., Yao, Y., Ping, J.F., Ying, Y.B., 2017b. Biosens. Bioelectron. 91, 504–514.
Le, M.H., Jimenez, C., Chainet, E., Stambouli, V., 2015. Sensors 15, 10686–10704.
Lei, Y., Wang, K., Wu, S.Y., Huang, D.D., Dai, M., Zheng, Y.J., Sun, Z.L., Chen, Y.Z., Lin, X.H., Liu, A.L., 2018. Biosens. Bioelectron. 112, 170–176.
Lekei, E.E., Ngowi, A.V., London, L., 2016. Environ. Health 15, 118.
Li, B.M., Yu, Q.L., Duan, Y.X., 2015. Crit. Rev. Biotechnol. 35, 82–93.
Li, D.Q., Qiao, X.G., Lu, J.X., Xu, Z.X., 2018a. Adv. Polym. Tech. 37, 968–976.
Li, F.L., Guo, Y.M., Wang, X.Y., Sun, X., 2018a. Biosens. Bioelectron. 115, 7–13.
Li, F.L., Wang, X.Y., Sun, X., Guo, Y.M., 2018b. Sens. Actuators B-Chem. 265, 217–226.
Li, J., Lu, J.X., Qiao, X.G., Xu, Z.X., 2017. Food Chem. 221, 1285–1290.
Li, S., Li, J., Luo, J., Xu, Z., Ma, X., 2018d. Mikrochim. Acta 185, 295 (UNSP).
Li, S., Wu, X., Liu, C., Yin, G., Luo, J., Xu, Z., 2016a. Anal. Chim. Acta 941, 94–100.
Li, T.J., Ding, B.Q., Zhou, C.X., Li, D.Q., 2018e. J. Biobased Mater. Biol. 12, 525–531.
Li, X., Zhou, B., Zhao, Z.L., Hu, Z.X., Zhou, S.F., Yang, N., Huang, Y., Zhang, Z.H., Su, J., Lan, D., Qin, X., Meng, J.Y., Zheng, D., He, J., Huang, X.N., Zhao, J., Zhang, Z.Y., Tan, W.H., Lu, X.L., Zhao, Y.X., 2016b. J. Biomed. Nanotechnol. 12, 2151–2160.
Li, X.Y., Li, J.J., Zhu, C.X., Zhang, X.H., Chen, J.H., 2018f. Talanta 182, 292–298.
Li, X.Z., Zhang, S., Yu, Z., Yang, T.Y., 2014. Appl. Spectrosc. 68, 483–487.
Liao, Z., Wang, J., Zhang, P., Zhang, Y., Miao, Y., Gao, S., Deng, Y., Geng, L., 2018. Biosens. Bioelectron. 121, 272–280.
Lin, B., Yu, Y., Li, R., Cao, Y., Guo, M., 2016. Sens. Actuators B-Chem. 229, 100–109.
Liu, B., Feng, J.H., Sun, X., Sheng, W., Zhang, Y., Wang, S., 2018a. Food Anal. Method. 11, 119–127.
Liu, K.K., Dong, H.M., Deng, Y., 2016a. J. Nanosci. Nanotechnol. 16, 6648–6656.
Liu, M., Hu, P., Zhang, G., Zeng, Y., Yang, H.W., Fan, J., Jin, L., Liu, H.N., Deng, Y., Li, S., Zeng, X., Elingarami, S., He, N.Y., 2015. Theranostics 5, 71–85.
Liu, M., Wang, Z.F., Tan, T., Chen, Z.S., Mou, X.B., Yu, X.C., Deng, Y., Lu, G.M., He, N.Y.,

2018a. Theranostics 8, 5772–5783.
Liu, M., Yang, T., Chen, Z.S., Wang, Z.F., He, N.Y., 2018b. Biomater. Sci. 6, 3152–3159.
Liu, M., Yu, X.C., Chen, Z., Yang, T., Yang, D.D., Liu, Q.Q., Du, K.K., Li, B., Wang, Z.F., Li, S., Deng, Y., He, N.Y., 2017a. J. Nanobiotechnol. 15, 81.
Liu, X., Li, Y., Liang, J., Zhu, W., Xu, J., Su, R., Yuan, L., Sun, C., 2016b. Talanta 160, 99–105.
Liu, Y., Deng, Y., Li, T.T., Chen, Z., Chen, H., Li, S., Liu, H.N., 2018a. J. Biomed. Nanotechnol. 14, 2156–2161.
Liu, Y., Lai, Y.X., Yang, G.J., Tang, C.L., Deng, Y., Li, S., Wang, Z.L., 2017b. J. Biomed. Nanotechnol. 13, 1253–1259.
Liu, Y., Liu, K.K., Dong, H.M., Zhang, L.M., Deng, Y., Ma, C., Wang, Z.L., 2016c. Nanosci. Nanotechnol. Lett. 8, 785–790.
Liu, Y., Lv, B., Liu, A., Liang, G., Yin, L., Pu, Y., Wei, W., Gou, S., Liu, S., 2018b. Sens. Actuators B-Chem. 265, 675–681.
Liu, Y., Wei, M., 2014. Food Control. 36, 49–54.
Lu, G., Crihfield, C.L., Gattu, S., Veltri, L.M., Holland, L.A., 2018. Chem. Rev. 118, 7867–7885.
Madianos, L., Skotadis, E., Tsekenis, G., Patsiouras, L., Tsigkourakos, M., Tsoukalas, D., 2018a. Microelectron. Eng. 189, 39–45.
Madianos, L., Tsekenis, G., Skotadis, E., Patsiouras, L., Tsoukalas, D., 2018b. Biosens. Bioelectron. 101, 268–274.
Meini, N., Farre, C., Chaix, C., Kherrat, R., Dzyadevych, S., Jaffrezic-Renault, N., 2012. Sens. Actuators B-Chem. 166, 715–720.
Meng, H.M., Fu, T., Zhang, X.B., Tan, W.H., 2015. Natl. Sci. Rev. 2, 71–84.
Meng, H.M., Liu, H., Kuai, H.L., Peng, R.Z., Mo, L.T., Zhang, X.B., 2016. Chem. Soc. Rev. 45, 2583–2602.
Montemurro, M., Pinto, L., Veras, G., Gomes, A.D., Culzoni, M.J., de Araujo, M.C.U., Goicoechea, H.C., 2016. Talanta 154, 208–218.
Muehlethaler, C., Leona, M., Lombardi, J.R., 2016. Anal. Chem. 88, 152–169.
Musumeci, D., Platella, C., Riccardi, C., Moccia, F., Montesarchio, D., 2017. Cancers 9, 174.
Nie, Y.H., Teng, Y.J., Li, P., Liu, W.H., Shi, Q.W., Zhang, Y.C., 2018. Spectrochim. Acta A. Mol. Biomol. Spectrosc. 191, 271–276.
Obana, H., Okihashi, M., Akutsu, K., Kitagawa, Y., Hori, S., 2002. J. Agr. Food Chem. 50, 4464–4467.
Ouyang, H., Tu, X.M., Fu, Z.F., Wang, W.W., Fu, S.F., Zhu, C.Z., Du, D., Lin, Y.H., 2018. Biosens. Bioelectron. 106, 43–49.
Pang, S., Labuza, T.P., He, L.L., 2014. Analyst 139, 1895–1901.
Pedersen, B., Ssemugabo, C., Nabankema, V., Jors, E., 2017. Environ. Health Insights 11 (UNSP 1178630217713015).
Peng, Y.G., Zhang, D.D., Li, Y., Qi, H.L., Gao, Q., Zhang, C.X., 2009. Biosens. Bioelectron. 25, 94–99.
Pieczonka, N.P.W., Aroca, R.F., 2008. Chem. Soc. Rev. 37, 946–954.
Prabhakar, N., Thakur, H., Bharti, A., Kaur, N., 2016. Anal. Chim. Acta 939, 108–116.
Priyadarshini, E., Pradhan, N., 2017. Sens. Actuators B-Chem. 238, 888–902.
Qi, Y., Xiu, F.R., Zheng, M., Li, B., 2016. Biosens. Bioelectron. 83, 243–249.
Qin, X.L., Yin, Y., Yu, H.J., Guo, W.J., Pei, M.S., 2016. Biosens. Bioelectron. 77, 752–758.
Rapini, R., Cincinelli, A., Marrazza, G., 2016. Talanta 161, 15–21.
Rapini, R., Marrazza, G., 2017. Bioelectrochemistry 118, 47–61.
Razmi, N., Baradaran, B., Hejazi, M., Hasanzadeh, M., Mosafer, J., Mokhtarzadeh, A., de la Guardia, M., 2018. Biosens. Bioelectron. 113, 58–71.
Sabela, M., Balme, S., Bechelany, M., Janot, J.M., Bisetty, K., 2017. Adv. Eng. Mater. 19, 1700270.
Sackmann, E.K., Fulton, A.L., Beebe, D.J., 2014. Nature 507, 181–189.
Safaa, E.K., 2011. Trop. Med. Int. Health 16 (271-271).
Sergelen, K., Liedberg, B., Knoll, W., Dostalek, J., 2017. Analyst 142, 2995–3001.
Sharma, R., Ragavan, K.V., Thakur, M.S., Raghavarao, K.S.M.S., 2015. Biosens. Bioelectron. 74, 612–627.
Shi, C., Liu, X.Y., Song, L.Y., Qiao, X.G., Xu, Z.X., 2015a. Food Anal. Method. 8, 2496–2503.
Shi, H., Zhao, G., Liu, M., Fan, L., Cao, T., 2013a. J. Hazard. Mater. 260, 754–761.
Shi, H.Y., Chen, N., Su, Y.Y., Wang, H.Y., He, Y., 2017. Anal. Chem. 89, 10279–10285.
Shi, J.Y., Chan, C.Y., Pang, Y.T., Ye, W.W., Tian, F., Lyu, J., Zhang, Y., Yang, M., 2015b. Biosens. Bioelectron. 67, 595–600.
Shi, Y., Dai, H.C., Sun, Y.J., Hu, J.T., Ni, P.J., Li, Z., 2013b. Analyst 138, 7152–7156.
Song, Y.J., Wei, W.L., Qu, X.G., 2011. Adv. Mater. 23, 4215–4236.
Song, Y.J., Zhao, C., Ren, J.S., Qu, X.G., 2009. Chem. Comm. 15, 1975–1977.
Songa, E.A., Okonkwo, J.O., 2016. Talanta 155, 289–304.
Sun, Y., Lu, J.Z., 2018. Luminescence 33, 1298–1305.
Tang, T., Deng, J., Zhang, M., Shi, G., Zhou, T., 2016. Talanta 146, 55–61.
Tang, Y.J., Zou, J., Ma, C., Ali, Z., Li, Z.Y., Li, X.L., Ma, N.G., Mou, X.B., Deng, Y., Zhang, L.M., Li, K., Lu, G.M., Yang, H.W., He, N.Y., 2013. Theranostics 3, 85–92.
Toh, S.Y., Citartan, M., Gopinath, S.C.B., Tang, T.H., 2015. Biosens. Bioelectron. 64, 392–403.
Vasilescu, A., Marty, J.L., 2016. Trac-Trend Anal. Chem. 79, 60–70.
Velu, R., Frost, N., DeRosa, M.C., 2015. ChemComm 51, 14346–14349.
Vendrell, M., Maiti, K.K., Dhaliwal, K., Chang, Y.T., 2013. Trends Biotechnol. 31, 249–257.
Verdian, A., 2018. Talanta 176, 456–464.
Wang, J.H., Lu, P., Yan, J.N., Zhang, Y.F., Huang, L.Y., Ali, Z.S., Liu, B., Li, Z.Y., He, N.Y., 2016. J. Biomed. Nanotechnol. 12, 710–716.
Wang, J.L., Wu, Y.G., Zhou, P., Yang, W.P., Tao, H., Qiu, S.Y., Feng, C.W., 2018a. Analyst 143, 5151–5160.
Wang, L., Liu, X., Zhang, Q., Zhang, C., Liu, Y., Tu, K., Tu, J., 2012. Biotechnol. Lett. 34, 869–874.
Wang, M.L., Yue, D.F., Qiao, Q.L., Miao, L., Zhao, H.D., Xu, Z.C., 2018b. Chin. Chem. Lett. 29, 703–706.
Wang, P., Wan, Y., Ali, A., Deng, S., Su, Y., Fan, C., Yang, S., 2015. Sci. China Chem. 59, 237–242.
Wei, M., Feng, S., 2017. Microchim. Acta 184, 3461–3468.
Williams, R.M., Crihfield, C.L., Gattu, S., Holland, L.A., Sooter, L.J., 2014a. Int. J. Mol. Sci. 15, 14332–14347.
Williams, R.M., Kulick, A.R., Yedlapalli, S., Battistella, L., Hajiran, C.J., Sooter, L.J., 2014b. J. Nucleic Acids 2014, 102968.
Wu, X.Z., Li, W.F., Guo, P.R., Zhang, Z.X., Xu, H.H., 2018a. J. Agr. Food Chem. 66, 3966–3974.
Wu, Y.Y., Li, X.Y., Tan, X.C., Feng, D.F., Yan, J., Zhang, H., Chen, X., Huang, Z.Y., Han, H.Y., 2018b. Electrochim. Acta 282, 672–679.
Xi, Z.J., Huang, R.R., Deng, Y., He, N.Y., 2014. J. Biomed. Nanotechnol. 10, 3043–3062.
Xi, Z.J., Huang, R.R., Li, Z.Y., He, N.Y., Wang, T., Su, E.B., Deng, Y., 2015. ACS Appl. Mater. Interfaces 7, 11215–11223.
Xu, M.L., Gao, Y., Han, X.X., Zhao, B., 2017. J. Agr. Food Chem. 65, 6719–6726.
Xu, M.L., Liu, J.B., Lu, J., 2014. Appl. Spectrosc. Rev. 49, 97–120.
Yan, X., Li, H., Su, X., 2018. Trac-Trend Anal. Chem. 103, 1–20.
Yan, Z.D., Gan, N., Li, T.H., Cao, Y.T., Chen, Y.J., 2016. Biosens. Bioelectron. 78, 51–57.
Yang, L., Zhang, X.B., Ye, M., Jiang, J.H., Yang, R.H., Fu, T., Chen, Y., Wang, K.M., Liu, C., Tan, W.H., 2011. Adv. Drug Deliv. Rev. 63, 1361–1370.
Yang, M.Y., Xi, X.F., Wu, X.L., Lu, R.H., Zhou, W.F., Zhang, S.B., Gao, H.X., 2015. J. Chromatogr. A 1381, 37–47.
Yang, S.H., Zhang, F.F., Wang, Z.H., Liang, Q.L., 2018. Biosens. Bioelectron. 112, 186–192.
Yazdian-Robati, R., Hedayati, N., Ramezani, M., Abnous, K., Taghdisi, S.M., 2018. Nanomed. J. 5, 1–5.
Yellen, G., Mongeon, R., 2015. Curr. Opin. Chem. Biol. 27, 24–30.
Yu, H., Han, J., An, S.J., Xie, G., Chen, S.P., 2018. Biosens. Bioelectron. 109, 63–69.
Yue, G.Z., Su, S., Li, N., Shuai, M.B., Lai, X.C., Astruc, D., Zhao, P.X., 2016. Coord. Chem. Rev. 311, 75–84.
Zhan, S.S., Liu, X.F., Qin, J.A., Yang, M.H., Zhao, H.Z., Wang, Y., Guo, W.Y., Ma, Z.J., Kong, W.J., 2017. J. Chromatogr. B 1068, 233–238.
Zhang, C., Wang, L., Tu, Z., Sun, X., He, Q., Lei, Z., Xu, C., Liu, Y., Zhang, X., Yang, J., Liu, X., Xu, Y., 2014. Biosens. Bioelectron. 55, 216–219.
Zhang, Q., Li, L.Y., Qiao, Z.H., Lei, C.Y., Fu, Y.C., Xie, Q.J., Yao, S.Z., Li, Y.B., Ying, Y.B., 2017. Anal. Chem. 89, 12145–12151.
Zhao, C.L., Hua, M., Yang, C.Y., Yang, Y.H., 2017. Chin. Chem. Lett. 28, 1417–1423.
Zhong, Q.S., Shen, L.L., Liu, J.Q., Yu, D.B., Li, S.M., Yao, J.T., Zhan, S., Huang, T.H., Hashi, Y., Kawano, S., Liu, Z.F., Zhou, T., 2016. J. Chromatogr. A 1442, 53–61.
Zhou, B.C., Yang, H.W., Deng, Y., Liu, M., Liu, B., He, N.Y., Li, Z.Y., 2016. Sci. China Chem. 59, 1051–1058.
Zhou, W.Z., Huang, P.J.J., Ding, J.S., Liu, J., 2014. Analyst 139, 2627–2640.
Zhu, X., Kou, F.X., Xu, H.F., Han, Y.J., Yang, G.D., Huang, X.J., Chen, W., Chi, Y.W., Lin, Z.Y., 2018. Sens. Actuators B-Chem. 270, 263–269.