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Aptamer based tools for environmental and therapeutic monitoring: A review of developments, applications, future perspectives

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ABSTRACT

Nucleic acids in the form of aptamers play a growing and significant role in the targeted and rapid analysis of environmental sample composition and medical analyses. In this paper, the review of both aptamers synthesis methods as well as application of these short chain oligonucleotides (with critical comments on their strong and weak features) are given. The first ones include: systematic evolution of ligands by exponential enrichment (SELEX), high throughput aptamer identification screen (HAPIscreen), and a non-equilibrium capillary electrophoresis of equilibrium mixture (NECEEM). Afterwards, manuscript describes variety of sensors and biotests utilizing aptamers as active part of its action starting from electrochemical aptasensors, through optical to piezo-electric ones. Described biotests present basic developments in enzyme-linked apta-sorbent assays (ELASA) that can be performed with different variations (enzyme-linked aptamer assay (ELAA), enzyme-linked oligonucleotide assay (ELONA) and aptamer-linked immobilized sorbent assay (ALISA)). Next, the review presents advantages and drawbacks of recent aptameric developments in versatile laboratory applications, namely medical ones, as well as analytical and bioassays. Utilitarian development of aptasensors and aptamers would strongly benefit from an assembly of interdisciplinary teams containing chemists, physicists, biologists, medical doctors, and material and electronic scientists, to determine the most effective application methodologies.

KEYWORDS

Aptamer; aptasensors; SELEX; HAPIscreen; NECEEM; ELONA; ELASA

1. Introduction – current challenges in analysis of environmental and biological samples

While over the past decades, significant advances have been made in the field of chemical and biological analysis, yet, low-cost, reliable, rapid, highly precise, sensitive, specific and targetoriented (to compounds bacteria,

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viruses, proteins, antibodies and others, at low concentration levels) analyses remain a challenge for researchers. Correct analysis usually begins with proper sampling and transportation, these stages are crucial and even the best-performed analysis will be of no value, if these steps are poorly carried out. Badly collected samples will not be representative and poorly preserved or examined after a significant period will not reflect the average composition of a given studied object (Csuros 2018).

Determination of different types of analytes (simple organic and inorganic chemicals as well as macromolecular structures such as proteins or even cells) requires subjecting the sample to additional preparation stages such as purification, extraction, isolation and enrichment. At each of these stages, contamination or alteration of analyte concentration may occur (e.g. by loss of sample volume, absorption of the analyts on the walls of laboratory vessels, aggregation of the determined proteins etc.), these phenomena can be a significant obstacle in obtaining the correct result in the trace analysis.

All these stages significantly extend time of the analysis, increase costs and consumption of reagents (often very toxic to the environment). Some samples require special treatment, their composition can be variable over time as in the case of body fluids such as blood, the longer the path of the samples from the point of collection to the laboratory, the greater is the risk of changes in their properties and therefore the risk of diagnostic error (Singh, Graber, & Hofer, 2016). To face this challenges there is a great dement for creating innovative analytical devices characterized by high precision, sensitivity, specificity, speed, and usability (e.g. portable devises) for monitoring a growing number of environmental pollutants as well as for medical applications (Long, Zhu, & Shi, 2013).

In this paper authors focused on a critical evaluation on how to the use aptamers as semi-universal tools for recognizing different types of analytes and their usefulness in defeating challenges related to sample analysis.

2. Aptamers – their properties, mode of actions and methods of production

Aptamers are short-chain oligonucleotides of RNA or singlestranted DNA (usually in the range of 40 to 100 nucleotides) and were simultaneously described for the first time by three groups of scientists: Tuerk and Gold (1990), Robertson and Joyce (1990), and Ellington and Szostak (1990). The uniqueness of aptamers lies in their high affinity, and is a result of their flexibility and the ability to fold upon binding with a target; hence their name, derived from the Latin *aptus* – fit, attached or joined and the Greek

Table 1. Differences between antibodies and aptamers (Nezlin, 2014; Toh et al., 2015).

Features	Aptamers	Antibodies
Molecule size	Minimal size is 10 kDa	Minimal size is ca. 180 kDa
Production/development	*Via* chemical synthesis and selection resulting in less batch variation an shorter time of production	Laboratory animals are used, what affects the batch to batch variation and longer time of production
Immobilization	Through adsorption or chemical coupling	Immobilization by biotin/streptavidin or chemical coupling
Production conditions	Necessity to use highly purified immmunoantigen for selection	Immunoantigens administered to animals do not need to be purified
Costs	Less expensive than production of antibodies, however, it is still expensive	Large costs result from the use of laboratory animals, the difference in batches and their storage conditions
Possibility of storage	More stable in higher temperatures and posse a longer shelf life compared to antibodies.	Can be irreversibly denatured at room temperature
Chemical modification of aptamer/antibody	Can be manipulated chemically and labeled without losing specificity	Labeling may reduce the affinity of antigens towards targets
Toxicity/immunotoxicity	There is no immunological response of the organisms to aptamers	Possibility of inducing an immune response in the patients
Activity in different environments	Active in different reaction environments	Active only in a physiological environment

meros – part. (Tuerk & Gold, 1990; Robertson & Joyce, 1990; Ellington & Szostak, 1990; Ng et al., 2006; Nezlin 2014).

Aptamers act as ligands, binding strongly with the target molecule as evidenced by the nano- or pico-molar dissociation constant $\left(K_d = \frac{[free\ \ aptamer]\cdot[free\ \ target]}{[aptamer-target\ \ complex]}\right)$ of the resulting target-aptamer complex, which can exhibit a greater affinity for the target than the antibodies, that were so far considered highly selective. Unlike antibodies, aptamers are obtained during chemical synthesis (completely different than in the case of antibodies that are obtained using laboratory animals); in addition, they retain their properties both during storage and in different reactionary environments. Additional information on the differences between aptamers and antibodies are summarized in Table 1 (Nezlin 2014; Toh, Citartan, Gopinath, & Tang, 2015).

Molecular recognition of target molecules by aptamers may occur between different secondary and tertiary structures. For example, small molecule compounds, such as amino acids, combine with aptamers using pseudoknots, internal loops, and one-sided bulges for interaction (Figure 1) (Antunes, Jorge, Caffarena, & Passetti, 2018). In the case of large molecules, different types of reactions and physical factors are involved in the formation of aptamer-target complexes, including hydrogen bonds, polar groups, shapes, and van der Waals forces as indicated by nuclear magnetic resonance studies (Figure 1) (Song, Wang, Li, Fan, & Zhao, 2008). All of these interactions result in a permanent 'fitting' of the aptamer-ligand to a given biomolecule, or *vice versa*, if the oligonucleotide is larger than its target

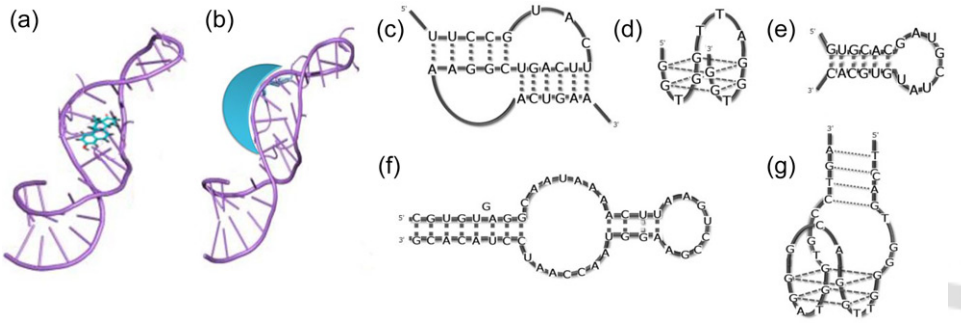

Figure 1. Three-dimensional structure of aptamer with bonded analyte e.g. a) small molecule, b) large molecule and schematic secondary structures of aptamers: c) pseudoknot, d) G-quartet, e) hairpin, f) stem-loop/bugle, g) G-quadruplex, adapted from (Nezlin, 2014; McGown, Joseph, Pitner, Vonk, & Linn, 1995; Radom et al., 2013; Deng et al., 2014; Jo & Ban, 2016). G, guanine; C, cytosine; A, adenine; T, thymine; U, uracile.

Aptamers can bind to a wide range of enzymes, regulatory proteins, growth factors, mono- and polyclonal antibodies (Hayat & Marty, 2014), lectins as well as low molecular weight vitamins (Selvakumar & Thakur, 2012), antibiotics, organic pigments, amino acids, peptides, nucleotides (Tombelli, Minunni, & Mascini, 2005), tissues and organisms (Pereira et al., 2018), cells (Chen et al., 2016) and even some metal ions (Zhang, Liu, Guo, & Lin, 2018) (Figure 1; Tereshko, Skripkin, & Patel, 2003; Radom, Jurek, Mazurek, Otlewski, & Jeleń, 2013, Long, Long, White, & Sullenger, 2008).

Large quantities of aptamers can be obtained by biochemical synthesis most frequently by Systematic Evolution of Ligands by EXponential enrichment (SELEX). Additional methods include a high throughput aptamer identification screen (HAPIscreen), and a non-equilibrium capillary electrophoresis of equilibrium mixture (NECEEM) (Dausse et al., 2011; Toh et al., 2015; Berezovski et al., 2005). Aptamers, despite their advantages and versatility, also have disadvantages that may limit their usefulness; these limitations are enumerated in the Table 2.

It is possible to integrate aptamers with various platforms and transducers that will convert the signal from aptamers bounded with analytes to fluorescent, colorimetric, or electrochemical signals that are measurable and dependent upon the sample analyte concentration. Although most aptamer development is focused on medical applications (blood or human serum measurements), there are new achievements in environmental field. Commercially produced aptamers are available from multiple suppliers (Aptagen LLC, BasePair Biotechnologies Inc., AptaMatrix Inc.) which provide services for adjusting the sensitivity and structure of produced aptamers, but for now, there are no aptamer based commercial tests or biosensors dedicated to environmental pollution (Aptagen LLC, 2019; BasePair Biotechnologies Inc., 2019; AptaMatrix Inc., 2019).

Table 2. Advantages and disadvantages of aptamers application (Keefe et al., 2010; Rimmele, 2003; Cheng, Chen, Lennox, Behlke, & Davidson, 2013; Mascini, 2009; Crivianu-Gaita & Thompson, 2016; Nguyen et al., 2014, Palchetti & Mascini, 2008, Amiri et al., 2017).

Advantages	Disadvantages
• Small size: allows penetration of the tissue or passing through barriers such as the blood-brain barrier. • Nucleic acids prefer forming secondary structures resulting in significant number of receptor conformations. • Specificity to the target molecule, which is often at the antibody level. • Possible *in vitro* tests as well as *in vivo*. • Lack or low immune response and no toxicity. • Lower cost of production compared to competing antibodies. • The production proceeds *in vitro*, so there is no possibility of contamination with biological toxic factors that can induce immune response. • Aptamers are chemical synthesis without cell culture or animals, which eliminates ethical concerns. • High molecular stability (DNA is more stable than proteins) – resistance to temperatures and factors damaging proteins and the ability to easily renaturation, after disturbing the spatial structure. • A very large variety of target molecules ranging from small inorganic ions to cells. • Are able to renature and regain analyte binding ability after denaturation (possibility of multiple usages). • Low detection limits (even at zmol L^{-1} levels).	• Small size: aptamers can be easily rinsed out of the body, therefore, it is necessary to use modifications (or higher concentration) in order to prolong their presence in the human body. • Sensitive to nuclease degradation, this forces the use of phosphate backbone modifications. • Some targets due to the lack of functional groups or other properties will not bond with aptamers. • Bonds with target molecules are usually weaker than antibodies. • Aptamers can be easily digested by enzymes. • Due to the fact that it is still constantly evolving branch of science costs can be large in comparison to conventional methods. • Sequence determination *via* SELEX is still slow. • Around one-third of the target surface may be lost or unavailable after immobilization of the target molecule. • Immobilization steps can be unsuitable for small molecular targets, in particular when molecules have no functional groups.

2.1. Methods for generating aptamer sentences

2.1.1. SELEX

SELEX *in vitro* selection is the most widely used method for obtaining RNA and single strand DNA (ssDNA) aptamers with the desired physical and chemical properties. In the first step, a very large library of oligonucleotides is synthesized, consisting of randomly generated sequences and shapes of constant length surrounded by 5′ and 3′ ends. During the synthesis of different regions, monomer concentrations (pyridine and purine bases A, T/U, G, and C) in the reaction mixture are equimolar, so the probability of occurrence for each oligonucleotide combination is the same. In the case of n-nucleotide fragments, this gives 4^n different combinations; a pool of oligonucleotides that theoretically represent every possible nucleotide sequence (Groher & Suess, 2016).

The next step is incubation of the oligonucleotide library with the target molecule under specific conditions (pH, temperature and other) followed by elution. The target molecule is usually immobilized on a membrane. Sequences that specifically bind to the molecule are not removed by the following wash and are amplified by PCR (or by reverse transcription PCR in case of an RNA library) after elution from the target molecule. Obtaining

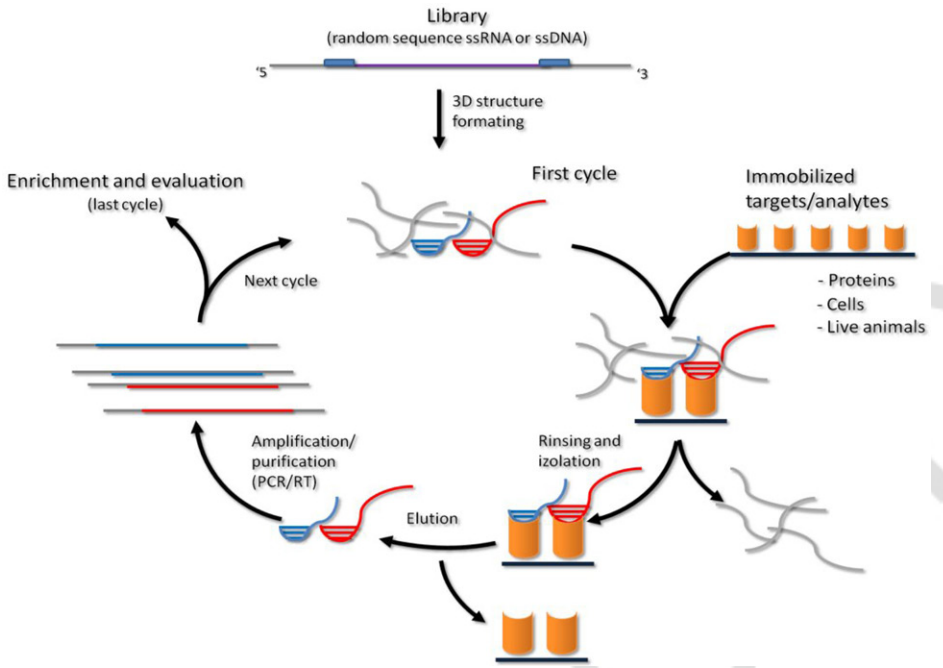

Figure 2. Schematic representation of basic SELEX (Klug & Famulok, 1994).

ssDNA after PCR amplification is the most critical step in the SELEX procedure. One method to prevent double strand DNA (dsDNA) formation is to use biotinylated reverse primers in the amplification step. Another method is asymmetrical PCR, which is performed with an excess amount of forward primer and very small amount of reverse primer. The selection process is repeated while gradually exacerbating the reaction conditions. During every amplification cycle and rinse, the participation of oligonucleotides that specifically recognize the target molecule increases (McKeague et al., 2015; Wei & Ling-Yun, 2009; Svobodová, Pinto, Nadal, & O' Sullivan, 2012). The last step of SELEX is duplication of the selected aptamers (see Figure 2 for details).

Then the oligonucleotides are tested for their binding strength (K_d) of the resulting complex and oligonucleotide affinities are determined; those characterized by the best performance are introduced into plasmids, cloned in bacterial cells, and sequenced. After learning the unique nucleotide sequence, multiple copies of the given aptamer are made by chemical synthesis. SELEX stages are presented schematically in Figure 2 (Klug & Famulok, 1994).

There are many variants of the SELEX method, including genomic SELEX to produce mirror aptamers (Spiegelmers), monoLEX, *in vivo*-SELEX, photo-SELEX, whole cell-SELEX, GO-SELEX, and *in silico*-SELEX.

This process is constantly being improved in order to shorten the process duration and to obtain aptamers with a very high affinity for different targets (Toh et al., 2015; Berezovski, Musheev, Drabovich, & Krylov, 2006; Wondergem, Schiessel, & Tompitak, 2017; Nguyen, Kwon, Kim, & Gu, 2014; Sefah, Shangguan, Xiong, O'donoghue, & Tan, 2010; Nitsche et al., 2007). Additional information about SELEX types are presented in Table 3. Unfortunatly, the SELEX approach is still relatively slow, can only be automated to a small degree, and is strongly biased, since efficiently amplified poor affinity binders may mask low copy/high affinity aptamers. The most time and labor-consuming step in developing aptamers is the affinity evaluation of the isolated oligonucleotide sequences prior to choosing the aptamer with the highest affinity.

2.1.2. Non-SELEX methods: HAPIscreen and NECEEM

HAPIscreen method is a non-SELEX method, which combines the target molecule and the potential aptamer with donor and acceptor microbeads. The aptamer interacts with the target molecule while simultaneously releasing a fluorescent signal produced by the microbeads, which is detected using a fluorescence reader (Dausse et al., 2011).

A precursor to HAPIscreen is the AlphaScreen® method (refer to Figure 3). The biological interaction between molecules closes the beads and further initiates a cascade of chemical reactions to obtain a greatly enhanced signal. After laser excitation, photosensitizers in the donor bead transform the surrounding oxygen into a more excited singlet state. The oxygen molecules disperse and react with a chemiluminescencer in the acceptor bead, which additionally activates the fluorophores that start to emit light at 520–620 nm wavelength. This type of aptamer screening allows for the selection of high-affinity aptamers within two hours (Dausse et al., 2011).

Another non-SELEX method is NECEEM, which consists of two major steps: incubation of the randomized DNA/RNA library with the target molecule, and separation of the formed complexes from the unbound nucleic acid ligands without the need for amplification. This is usually repeated three times until a pool of nucleic acids containing high affinity binders is obtained. Method principles rely on the assumption that when using high voltage unbounded targets, oligonucleotides will migrate at a different velocity than the target-aptamer complex It is assumed that the target molecule migrates faster than the oligonucleotide, and that the complex of the two has an averaged velocity. After t_0 time this initial mixture is divided into equivalent fractions (Figure 4; Krylov 2006; Kanoatov et al., 2015).

Table 3. Variations of SELEX processes used to produce aptamers.

Name	Basic features	References
Whole cell-SELEX	In Whole cell-SELEX process ssDNA library is incubated with the target cells (i.e. cancer cell). Bounded sequences are recovered from the cells by heating the complexes up to 95 °C, followed by centrifugation and amplified by PCR. The procedure, from design of oligonucleotides to enrichment of the selected pools, takes around 3 months.	Sefah et al., 2010
TECS-SELEX	TECS-SELEX utilizes cell-SELEX to select proteins ectopically expressed on the cell surface.	Ohuchi, Ohtsu, & Nakamura, 2006
MonoLEX	Method for the identification of a high-affinity DNA aptamers. A single step with use of affinity chromatography, followed by subsequent physical segmentation on the affinity resin and a single final PCR amplification step of bound aptamers.	Nitsche et al., 2007
Tailored SELEX	Allows selection of aptamers without sequence of primers. After each RNA selection cycle, the library is ligated with primers, reverse transcribed into complementary DNA (cDNA) and amplified by PCR. The reverse DNA strand is then cleaved by alkaline cleavage at a special site.	Vater, Jarosch, Buchner, & Klussmann, 2003
Conditional SELEX	Method enables the selection of aptamers that either can bind with the target only in the presence of a regulator molecule, or in contrary they can't bind to the target in the presence of regulator molecule.	Smith & Gold, 2004
MARAS	Magnetic-Assisted Rapid Aptamer Selection. Targeted protein is attached to magnetic nanoparticle, incubated with oligonucleotide library and subjected to rotation motion produced by an external magnetic field. This enables selection of high-affinity aptamers that remain bound with the target despite magnetic starring.	Lai & Hong, 2014
GenomicSELEX	Method for studying the network of nucleic acid–protein interactions within organisms. GenomicSELEX starts from libraries derived from genomic DNA. High-affinity binding RNAs are enriched from the initial pool through multiple rounds of binding of the RNAs to a given ligand.	Zimmermann, Bilusic, Lorenz, & Schroeder, 2010
Sol–gel SELEX	The method uses a specially fabricated advanced device utilizing microfluidics for aptamer selection. For protein immobilization, there are sol–gel arrays with droplets on the tops of individual microheaters of such microfluidics device used. After the target is immobilized, the solution containing oligonucleotide library is injected into the device and incubated with the target. Then each agarose droplet is individually heated and RNA aptamers are separately eluted, reverse transcribed to cDNA and amplified by PCR.	Bae et al., 2013
RAPID-SELEX	Combination of conventional SELEX and non-SELEX approaches. Cycle performed by standard SELEX protocol is followed by next SELEX round where the amplification step is not included. This method reduces time of aptamer selection in comparison with conventional SELEX while retaining the same affinity aptamer to the target molecule.	Szeto et al., 2013
MSD-SELEX-Particle Display selection	Primer is immobilize on beads through NHS-ester. Beads are mixed with an oligonucleotide library in water-in-oil droplets and then incubated with a target. Bound sequences are isolated, amplified followed by identification and analysis.	Zhu, Song, et al., 2014
In vivo-SELEX	In the method laboratory animals are used. Random RNA library is injected to laboratory animals (in reference study mice). Then aptamers are recovered and purified with DNase and RNase, amplify and re-injected. After 12 rounds (study data) negative selection was conducted.	Cheng et al., 2013
MAI-SELEX	Method to generate aptamers that specifically bind to different subunits of a protein. In the first stage target molecule is immobilized on magnetic bead followed by magnetic separation of the beads (5 rounds). Next, the aptamer pool from the first stage is incubated with the target, in which only one of the protein subunits is presented.	Gawande et al., 2017
Tissue slide-based SELEX	DNA library is incubated with slices of cancerous tissue. After incubation period, the complex of DNA with the cancer tissue is removed and the oligonucleotide sequences are used in PCR amplification. In the second round of selection, the PCR products are incubated with normal tissue slices as a counter selection step.	Zhang et al., 2015
SELEX-SAGE	The DNA library is incubated with proteins immobilized in 96-well plate, followed by washing, elution and PCR amplification of bound sequences. Amplified DNAs are sequenced using massively parallel single-molecule sequencing.	Djordjevic, 2007
GO-SELEX	DNA library is pre-incubated with the target, then added to the graphene oxide (GO), which adsorb unbounded ssDNA while bound DNA remains in the solution.DNA is separated from the target and amplified by PCR. After several cycles are subjected to selection, cloning and sequencing.	Nguyen et al., 2014
In silico-SELEX	Computer modeling using special software, to predict the outcome of the experiment under given conditions.	Wondergem et al., 2017

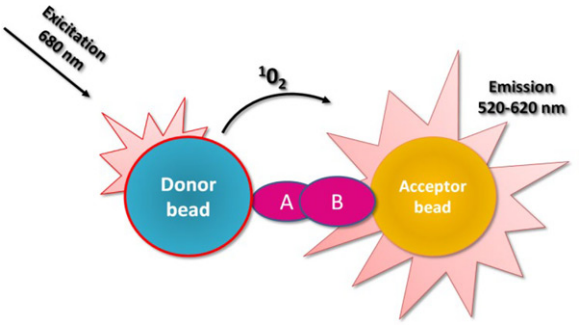

Figure 3. Diagram of AlphaScreen® test, components A and B represent the target molecules and the oligonucleotide (AlphaScreen®, 2018).

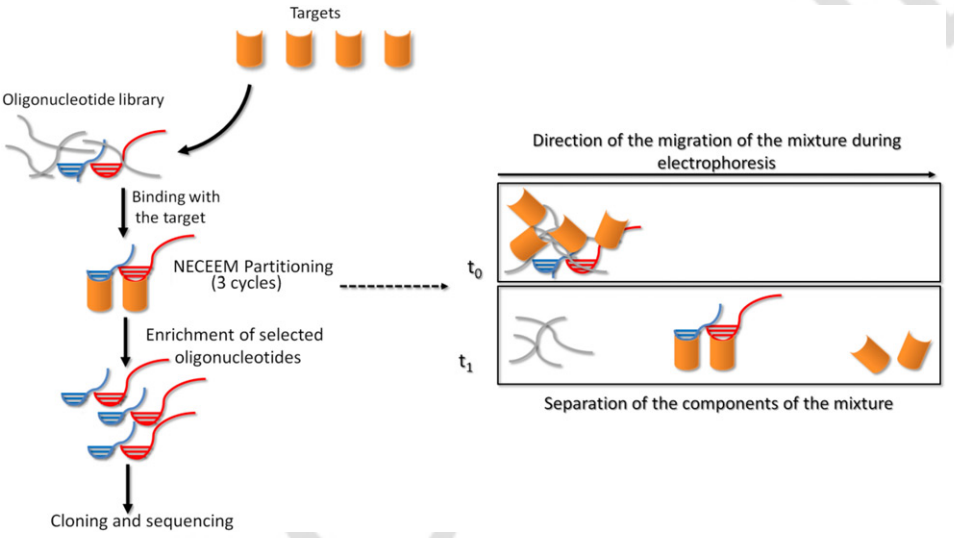

Figure 4. Diagram of the process of non-equilibrium capillary electrophoresis of equilibrium mixture (NASEEM) for receiving aptamers (Toh et al., 2015).

2.2. DNA and RNA libraries and their modifications

The vast amount and variety of nucleic acids make it possible to choose an aptamer for virtually any target. Calculations have shown that the optimal number of different sequences tested ranges from 10^{13} to 10^{15}. Both DNA and RNA can be used as aptamer bases; RNA enables intracellular expression, while DNA shows greater stability (Radom et al., 2013).

DNA and RNA libraries may contain sequences that surround the targeted aptamers to form a specific secondary structure, or include modified nucleotides that can greatly broaden the range of possible sequences. This may also affect aptamer properties, such as *in vivo* stability or resistance to RNAse and DNAse. Oligonucleotides can be easily modified by the substitution of one of the ribose hydroxyl groups with a methyl or an alkyl group

(Cummins et al., 1995). Alkylation of nucleic acids creates aptamers containing 2′-O-methylpyrimidine; such modified aptamers are more stable and more resistant to the attacks of exonuclease enzymes; similar action was observed with substitution of the ribose 2′-OH group with an amino group or fluorine atoms, which increased resistance to degradation by blood serum enzymes (Scaggiante et al., 2013; Nawrot & Sipa, 2006). Dimerization of selected aptamers allows for a fold-increase in affinity of the ligand to the molecule, and an increase in the durability of the complex formed that enables an increased number of binding sites. Therefore, it is possible to interact with more than one target molecule (Hasegawa, Taira, Sode, & Ikebukuro, 2008). Modification of phosphate residues by replacing them with sulfur atoms increases resistance to 3′-exonuclease digestion (Kaur, Rob, Caton-Williams, & Huang, 2013). Oligonucleotides can also be modified to show specificity to one of the enantiomers. For example, ribonucleases can recognize and hydrolyze only oligoribonucleotides based on a series of L-riboses (so-called mirror aptamers) (Klussmann, Nolte, Bald, Erdmann, & Fürste, 1996). Additionally, aptamers can be combined with fluorescent dyes, the so-called 'bridging' molecules that enable the aptamer to be labeled without losing its affinity, and preserving the fluorescent properties of the dye. Labeling in the vicinity of the intermolecular recognition region enables researchers to follow the conformational changes of the aptamer; after binding to the target molecule, the aptamer itself acts as a biosensor (Babendure, Adams, & Tsien, 2003).

3. Aptamer-based sensors and aptamer-based tests in environmental research and monitoring

3.1. Aptamer-based sensors (aptasensors)

Biosensor technology has developed quickly since the days of the first enzyme electrode for glucose detection described by Clark and Lyons in the 1960s; in particular, those containing aptamers suitable for binding very different targets, from micromolecules such as metals to macromolecules such as proteins, various test configurations have been designed and reported (Clark & Lyons, 1962). The combination of biological and electronic elements allows for quick, sensitive, and precise detection of not only small amounts of chemical compounds, but also dangerous microorganisms or toxins. The majority of these designs fall into either single-site or dual-site binding categories (Figure 5; Song et al., 2008).

Dual-site binding tests ('sandwich' tests) are one of the most commonly used formats, in which the analyte is surrounded by a pair of aptamers (Figure 5b). One is the capture probe, usually immobilized on the surface of solid supports (electrodes, glass chips, nanoparticles, or microparticles),

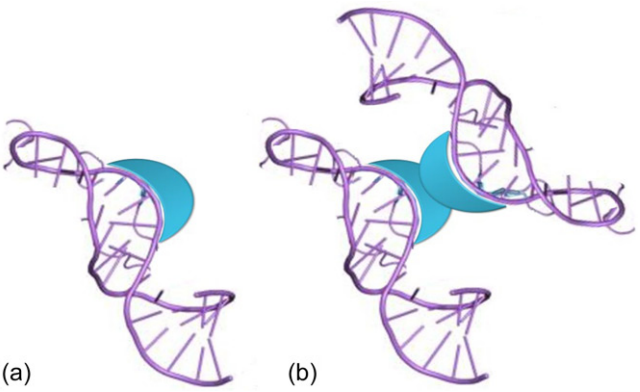

Figure 5. Single-site binding a) or dual-site binding b) aptamer-based types of test (Song et al., 2008).

and the other is a reporter probe, often conjugated to signal residues (fluorophores, enzymes, or nanoparticles) (Song et al., 2008). Measurement of biological phenomena occurring in the sensor can take place according to the transduction principle means of electrochemical (potentiometric, amperometric, and conductometric), optical (optical fiber and surface plasmon resonance biosensors, colorimetric, and fluorescent) and piezoelectric (mass sensitive including quartz crystal microbalance) detectors (Justino, Duarte, & Rocha-Santos, 2017).

3.1.1. Electrochemical aptasensors

Changes in the electrical field occur during redox reactions, and are measured by a transducer electrode. Electrochemical techniques are simple to use, fast, cost-effective, and are characterized by high selectivity and sensitivity. Most of them use label-free electrochemical impedance spectroscopy (EIS) or semiconductor field-effect sensors (FET), which show great promise, as they are not destructive. EIS is a frequency domain measurement made by applying a sinusoidal perturbation, often a voltage, to a system and in trasystors, in FET sensors, the interfacial potential between the sample and the gate is material depending on the target activity of the analyte measured (Kaisti, 2017; Muñoz, Montes, & Baeza, 2017). This is highly attractive for the detection of low-mass molecules and ions. In EIS, the change in electron transfer resistance is measured upon the aptamer binding to the target. The aptamer-target complex creates an isolating barrier on the electrode surface, and using FET sensors, the conductivity between two electrodes is gated by the change in surface potential that is induced by aptamer-target binding (Miranda-Castro, de-los-Santos-Álvarez, & Lobo-Castañón, 2017).

Most aptasensor electrode surfaces are coated with microwires formed of platinum (PtNPs), silver (AgNPs) and gold (AuNPs) nanoparticles or dotted carbon nanoparticles (GO, Graphene Oxide), on which aptamers are placed using various immobilization strategies and/or detection formats (Hayat & Marty, 2014; Zhang, Liu, et al., 2018). Flexible aptamers, which form three-dimensional structures upon binding with the target molecule, are immobilized on the electrode surface through chemisorption of thiol groups on Pt, Ag, Au, or C surfaces. This is followed by the creation of a self-assembled monolayer by the attachment of an amine-terminated aptamer to a thiol group, most often via the 3′ end, as this configuration seems to be more resistant to nuclease (Hayat & Marty, 2014; Yang, Yang, Pang, Vara, & Xia, 2015; Arroyo-Currás et al., 2017; Liu, Luo, et al., 2017). The aptamer may also be conjugated by covalent bonds to a chemically modified surface, most often hydroxyl, amino, or carboxylic acids, and less often with silicates or silicones (Zhu, Suter, White, & Fan, 2006; Actis et al., 2011; Taghdisi, Danesh, Emrani, Ramezani, & Abnous, 2015). Electroactive probes such as methylene blue (MB), ferrocene (Fc), $Fe(CN)_6^{4-/3}$ polymers containing ferrocene, and ruthenium complexes are more often used for the transduction of biological information into electroactive signals (Song, Lee, & Ban, 2012, Arroyo-Currás et al., 2017). Most of these methods have great potential however, there are, some limitations to eletrochemine aptasensors that use nanomaterials that arise from ntrinsic properties that may result in creating inefficient aptasensors (Jalalian, Karimabadi, Ramezani, Abnous, & Taghdisi, 2018).

MB and Fc are used both in labeled and non-labeled aptasensors (Figure 6a and b). In labeled aptasensors, the electrochemical aptasensor target induction causes the aptamer to stiffen into its three-dimensional structure, which interrupts electron exchange between the MB and the electrode surface, resulting in a decreased signal proportional to the amount of analyte. In the label-free version, an aptamer structure contains many MB probes that allow the flow of electrons. Changes in aptamer conformation upon target binding result in the release of all MB probes affecting the signal (Cao et al., 2017; Tao, Zhong-Yuan, Lian-Zhe, & Guo-Bao, 2011). In 'sandwich' type aptasensors, the target first binds to the aptamer immobilized on the electrode surface, and then the second aptamer binds to the target. Therefore, this type of test is useful for detecting molecules with two or more binding sites, such as proteins (Walter et al., 2012; Figure 6d).

Electrochemical aptasensors are already used to detect impurities in environmental samples from low molecular weight heavy metals to endocrine disrupting chemicals (EDC), antibiotics, and pesticides. Methods for utilization are constantly improved, as rapid and targeted determination of small molecule compounds such as heavy metals in environmental samples

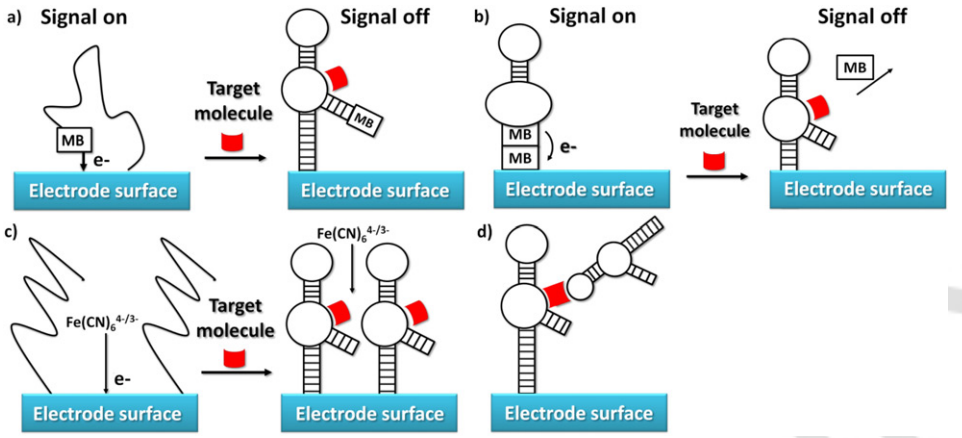

Figure 6. Labeled a) and label-free b) signal-off aptasensors. $Fe(CN)_6^{4-/3-}$ probe c) is prevented from reaching the electron surface by stiffened structure of the aptamer bonded with the target molecule. 'Sandwich' aptasensor d) – two aptamer bonded with one target molecule with more than one active place (Hayat & Marty, 2014, Mishra et al., 2018).

are very important for public health reasons. Intensive research is ongoing to develop very sensitive and selective aptamer biosensors to detect heavy metals at very low concentration levels.

Electrochemical aptasensors are used for the detection of heavy metals such as Hg^{2+}, Pb^{2+}, Cd^{2+}, and As^{3+}. In one approach, an ultra-sensitive and highly selective electrochemical label-free aptasensor was proposed for the quantitative detection of Hg^{2+} in zeptomolar (zmol L^{-1}) levels. In a customized sensor, Amiri, Navaee, Salimi, and Ahmadi (2017) substituted thiol groups in single-stranded DNA, which then self-assembled on a gold electrode surface through the S-Au interaction. Hybridization of ssDNA with complementary DNA (cDNA), and the consequences of dehybridization in the presence of Hg^{2+} were followed through differential pulse voltammetry responses using a redox probe ($[Fe(CN)_6]^{3-}/^{4-}$). An essential and desirable phenomenon for the detection of Hg^{2+} in environmental samples is the formation of a thymine–Hg^{2+}–thymine complex (Amiri et al., 2017; Mishra, Sharma, & Mishra, 2018).

In another aptameric study, Pb^{2+} ions were detected with sensors developed on the base of a carboxylic acid group in functionalized multi-walled carbon nanotubes and directly electrodeposited gold nanoparticles (GNPs). The DNA capture probe was self-assembled onto the surface of the modified electrode for hybridization with the guanine-rich aptamer probe to form a DNA double helix structure. Pb^{2+} ions added to the sample caused the DNA duplex to unwind, and formed a stabilized G-quadruplex due to the Pb^{2+}-induced G-rich DNA conformation. The aptasensor was able to detect lead ions at a 4.3 pmol L^{-1} detection limit (Zhu, Zeng, et al., 2014).

Furthermore, an ultrasensitive electrochemical aptasensor based on a glass carbon electrode modified with AuNPs, chitosan, and aptamers has been constructed to detect cadmium (II) ions. The presence of Cd^{2+} triggers a change in aptamer conformation, causing the Cd/Cd-aptamer complex to adsorb more electrochemical signal indicator $[Ru(NH_3)_6]^{3+}$ than poly-(diallyl dimethyl ammonium chloride) (PDDA), which is applied to neutralize the Cd-aptamer *via* electrostatic interaction. Using differential pulse voltammetry (DPV) detection, the peak current increases along with the increase in Cd^{2+} concentration with a detection limit as low as 0.05 pmol L^{-1} (Liu, Lai, et al., 2017).

In another study, As^{3+} ions were detected using new thermally stable polyarylidene (azomethine-ether)s and copolyarylidene (azomethine-ether)s (PAAP) hybrids based on diarylidenecycloalkanone synthesis using a solution polycondensation method. A thin layer of PAAP was coated onto a flat glassy carbon electrode (GCE) using a conducting nafion (5%, CAS no. 66796-30-3) coating agent to fabricate a sensitive and selective As^{3+} ion aptamer with a short response time in a neutral buffer system. The detection limit was calculated at 6.8 ± 0.1 nmol L^{-1} (Rahman, Hussein, Aly, & Asiri, 2018). Tang, Wang, Yu, Zhang, and He (2018) presented an aptasensor containing a multi-channel one-time screen-operated carbon electrode (SPCE) using open circuit technology (OCP) for the simultaneous detection of three heavy metals, Hg^{2+}, Cd^{2+} and As^{3+}, with detection limits of 2.0, 0.62, and 0.17 pmol L^{-1}, respectively. More detailed review on possibility of using aptamers and nanomaterials can be found in work of Farzin, Shamsipur, and Sheibani (2017).

In addition to heavy metal identification, aptasensors can be used to identify pesticides, antibiotics, and even bisphenols. Fei et al. (2015) proposed a low-cost, selective, and sensitive electrochemical aptasensor using the direct impedimetric method to detect the pesticide acetamiprid in environmental samples. AuNPs with multiwalled carbon nanotube-reduced GO-nanoribbon composites were synthesized in a one-pot reaction (Au/MWCNT-rGONR). This unique composite was used as a platform to immobilize aptamers. This aptasensor was successfully used to determine pesticides of interest even when the sample contained interfering substances with a detection limit of 0.17 fmol L^{-1} (Fei et al., 2015).

Another label-free electrochemical aptasensor was constructed by Zhan et al. (2015) to detect tetracycline in dietary, environmental, and biological samples in a cost-efficient, sensitive, and selective manner. A suitable aptamer was immobilized on a composite consisting of reduced GO, magnetite (Fe_3O_4), and sodium alginate on the surface of a screen-printed carbon electrode (SPCE). Tetracycline could be quantified using DPV with a detection limit of 0.6 nmol L^{-1} (Zhan et al., 2016).

Similarly Cui et al. (2015) presented a label-free, single-step method for the detection of bisphenol A (BPA) in aqueous samples. An aptamer based molecular probe was immobilized on a commercially available array of interdigitated aluminum microelectrodes. To quantify the amount of BPA in the sample, the interfacial capacitance rate change caused by the specific binding between the analyte and the immobilized aptamer was measured. The sensor reached a detection limit as low as 10 fmol L^{-1}, with a 20 s response time. This inexpensive, highly sensitive, and rapid method is promising technology for the on-site detection of BPA in food and water samples (Cui et al., 2015).

Electrochemical aptasensors have also been used in the detection of pathogens such as *Salmonella*. A biosensor based on a glassy carbon electrode modified with GO and AuNPs was combined with specific aptamers. In order to quantify the content of *Salmonella* sp., the electrochemical impedance spectrum was measured. The more *Salmonella* was added to the test solution, the more the current between the electrode and the electrolyte was reduced, which enabled a detection limit of 3 colony forming units (CFU) mL^{-1}. This aptasensor is useful for detecting *Salmonella* species in water and food samples (Ma et al., 2014).

The use of eletrochermical aptasensors also can involve problems, unfortunately, these sensors are most often tetsted on spiked samples and there are few studies that would be carried out on real samples. The electrochemical methods themselves are sensitive to electromagnetic interference and there is a need for buffers to maintain the aptamer working environment (Zhang, Liu, et al., 2018).

3.1.2. Optical aptasensors (fluorescence and colorimetric sensors)

Fluorescence-based aptasensors are a type of optical sensor, which require a fluorophore (a fluorescent chemical compound) and a quencher (quenches fluorescence). These types of sensors arecurrently used with great success in indentification and quantification of environmental pollutants such as heavy metals ions (García-Gutiérrez, Huerta-Aguilar, Thangarasu, & Vázquez-Ramos, 2017).

In aptasensors the fluorophore part is attached to the other. In some cases, a surface made of a GO-sheet can act as quencher and adsorb the fluorophore-labeled aptamer in its unbound state. In other cases, the quencher is attached to a complementary DNA sequence (cDNA) which is unbound from the aptamer when the target molecule appears in the solution (Feng, Dai, & Wang, 2014). These types of aptasensors can be divided into signal-on and signal-off categories (Figure 7a–c), which increase or decrease the fluorescence signal upon binding with the target molecule. In signal-on sensors, the initial conformation of the aptamer maintains the

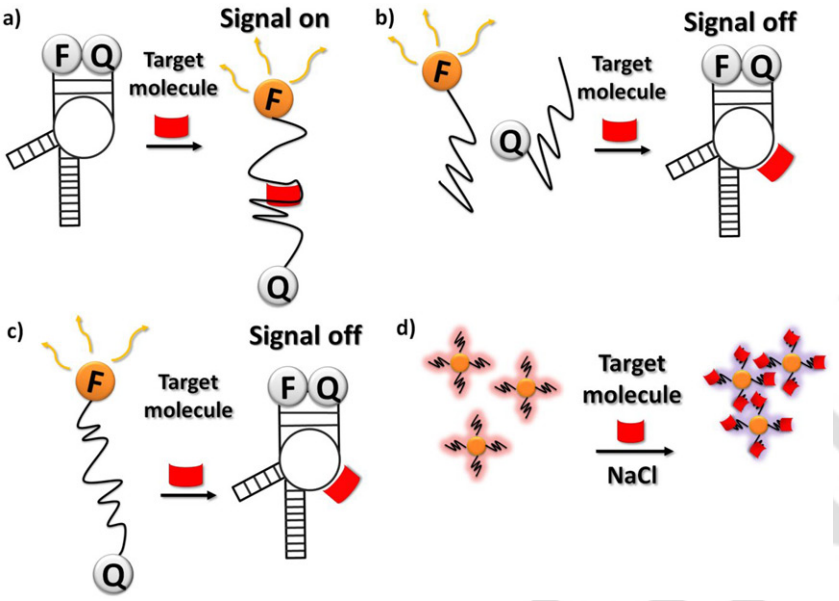

Figure 7. Schematic presentation of fluorescent aptasensor: signal-on presented in a), signal-off presented in b) and c) of fluorescent aptasensors. d) Binding targets by aptamers immobilized on AuNPs initiates their aggregation resulting in color change from red to blue (Song et al., 2012, Feng et al., 2014).

fluorophore and quencher very close to each other and results in a low fluorescence signal. Off and On fluorescent-based sensors had been for some time used with success in detection environmental pollution (García-Gutiérrez et al., 2017). Binding to the target molecule causes a change in the aptamer conformation and separates the fluorophore from the quencher, resulting in a higher fluorescence signal. In signal-off sensors, the coupling of fluorophore and quencher occurs when the target molecule appears in the solution. This decreases the fluorescence signal (correlated to the concentration of the target), which otherwise remains strong when the elements are separated (Akki & Werth, 2018).

Colorimetric tests are easy to perform, and their results can be measured and determined with uncomplicated equipment and in some cases, by the naked eye (Lu et al., 2013). Most colorimetric aptamer based tests are based on the principle that the visible color of AuNP suspensions change depending on the dispersion and aggregation in the solution. For example, if aptamers are immobilized on AuNPs stabilized in highly concentrated salts (e.g. NaCl), they are dispersed in the solution and prevent nanoparticle aggregation. This would turn the sample solution red. As soon as an aptamer recognized analyte appears in the solution, the aptamer is separated from the AuNPs, which then aggregate and cause the solution to turn blue (Figure 7d). Change and color intensity provide qualitative and

quantitative information about the presence and concentration sample analyte, and the blue shift range is quantified as the ratio of absorbance from 620 nm to 520 nm ($\sim A_{620}/A_{520}$ nm) (Akki & Werth, 2018).

The literature also describes colorimetric tests that change from blue to red after the analyte is introduced. For example, aptamer thiol groups are covalently bound to AuNPs and the secondary sequence of aptamer-AuNPs cause the aggregation of these complexes and turn the solution blue. Introduction of the target to the solution causes the molecules to disperse, which manifests as a color change to red. In some cases, a reactive chromogenic agent like tetramethylbenzidine (TMB) is used in conjunction with H_2O_2. TMB reacts on the surface of AuNPs, which serve as a catalyst to promote peroxidase-like activity. When the target molecule binds with aptamers, the AuNPs surface is released and can catalyze the oxidation of colorless TMB to form TMB-diimine, which changes the color from red to purplish-blue (Yuan, Zhao, Wang, & Quan, 2017; van den Kieboom et al., 2015). As with fluorescence-based aptasensors, colorimetric assays are successfully applied to detect analytes in tap and lake water, milk, soil, and wastewater samples. The only potential analytical obstacle to using tests containing AuNP particles as carriers is the sample matrix. This is why environmental samples are usually diluted in special buffers, and only those with a high salt content may be a problem (van den Kieboom et al., 2015). Additionaly, despite continuous improvement, there are still many difficulties in the functioning of these aptasensors such as pH, ionic strength, and temperature, viscosity and other external conditions. For some sensors there is a need for using different types of buffers that can affect the quality of the determination (Robati et al., 2016).

Small molecules such as heavy metal ions can be determined by optical sensors; for example, Qian, Shan, Chai, Chen, and Feng (2015) developed a fluorescent signal-on nanosensor for Pb^{2+} based on biocompatible graphene QDs (quantum dots), GO and an aptamer in G-quadruplex formation with a detection limit of 0.6 nmol L^{-1}. Another simple and reliable detector for As^{3+} in drinking water and blood serum was introduced by Taghdisi, Danesh, Ramezani, Emrani, and Abnous (2018). The presented sensor was the switch-on type. Upon introduction of As^{3+} to the solution, the label-free aptamer was immobilized on silica nanoparticles coated with a streptavidin surface and formed a hairpin structure, which strengthened the fluorescence signal with a very low detection limit of 0.45 nmol L^{-1} (Taghdisi et al., 2018).Lin, Yu, Li, Cao, and Guo (2016) and Yang, Qian, et al. (2015) presented two different fluorescent sensors to determine the presence of acetamiprid (Lin et al., 2016; Yang, Qian, et al., 2015). Lin et al. (2016) used an aptamer-modified ZnS:Mn probe constructed by combining ZnS:Mn QDs with an acetamiprid binding aptamer. Without the

presence of acetamiprid, the signal is switched off by means of multi-walled carbon nanotubes (MWCNTs) based on the fluorescence resonance energy transfer (FRET) between the ZnS:Mn-aptamer complex and the MWCNTs. FRET is a mechanism describing energy transfer between two light-sensitive molecules called chromophores (or fluorophores). Donor chromophore, when in its electronic excited state, may transfer energy to an acceptor chromophore through nonradiative dipole–dipole coupling in short range < 10 nm (Zal & Gascoigne, 2004).

Introduction of acetamiprid to the sample switches on the fluorescence signal by the specific combination of the aptamer and the target molecule with a detection limit of 0.7 nmol L^{-1}. This was satisfactorily used to detect pesticides in environmental samples (Lin et al., 2016). Additionally, Yang, Qian, et al. (2015) used hemin-functionalized reduced graphene oxide (hemin-rGO) composites, which adsorb the aptamer and hemin that catalyze 3,3,5,5-tetramethylbenzidine (TMB) in the presence of H_2O_2 to identify acetamiprid. At a suitable salt concentration, the proposed colorimetric aptasensor reached a detection limit of 40 nmol L^{-1} (Yang, Qian, et al., 2015).

FRET is also used to determine the presence of 17β-estradiol. An aptamer duplex consisting of a carboxyfluorescein (FAM)-labeled E2 and complementary DNA partially modified with Black Hole Quencher 1 (BHQ1) was used. After the introduction of 17β-estradiol into the sample to compete for binding sites with cDNA, cDNA released from the aptamer/DNA duplexes FAM fluorescence was recovered, and the fluorescent signal was switched on. This sensor has been successfully applied to detect 17β-estradiol in environmental, biological, and dietary samples with a 0.35 nmol L^{-1} detection limit (Zhang, Li, Zhang, & Chen, 2018). Samples tested with optical methods must maintain certain standards, they must be transparent and, if possible, colorless; additionally, the cost and durability of fluorescent markers must be taken into account.

3.1.3. Piezoelectric (mass-dependent) aptasensors

Piezoelectric aptasensors are less common than the previously mentioned types, however, they include sensors for detecting viruses, bacteria, and toxins. Mass-dependent sensors are label-free, have low noise and high sensitivity, and include acoustic wave-based sensors such as quartz crystal microbalance (QCM) and surface acoustic wave (SAW) sensors (Figure 8a), micromechanical cantilever-based sensors (Figure 8b), and surface-plasma resonance (SPR) sensors (Figure 8c) (van den Kieboom et al., 2015). The piezoelectric effect is based on reversible electro-mechanical interactions with substances that have crystalline materials and possesses an asymmetrical structure. The principle is that mechanical deformation causes voltage

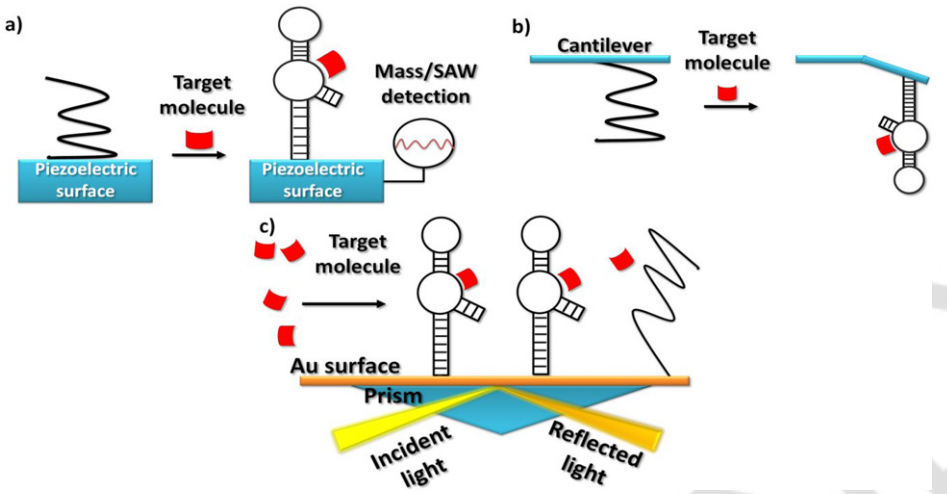

Figure 8. Piezoelectric aptamer based-sensor with wave-detection (QCM and SAW) a) microcantilever sensor b) and with SPR detection c) (Song et al., 2008).

tension on the material, and *vice versa*. The relationship between the two is always linear (Aksel & Jones, 2010; Song et al., 2008). Other piezoelectric aptasensors use SAWs. Such devices are constructed from piezoelectric materials on which electrodes made from inert metals or alloys are arranged in the shape of a comb. Applying voltage to the electrode generates a wave that propagates through the piezoelectric material, and this wave can be disrupted by an analyte bound with an aptamer (Mujahid & Dickert, 2017). The operational principle of cantilevered aptasensors is completely different from those described above. In cantilevered sensors, the aptamer is placed on the surface of a microcantilever, which deflects when the aptamer is weighted by the bound target molecule. Such deflection can be measured optically or electronically (Zhao, Jia, Wen, & Yu, 2017; Lim, Kouzani, & Duan, 2010). SPR devices are capable of registering mass changes by the associated change in the refractive index at the surface bound to the aptamer (Figure 8c). In this case, the sensor measures the resonance angle changes that occur on the molecular surface that are altered when the aptamer binds to the target molecule (Guo, 2012).

Wave based-aptasensors were used by Ozalp, Bayramoglu, Erdem, and Arica (2015) to detect the presence of pathogenic *Escherichia* in food and water samples at a 100 CFU mL^{-1} detection limit. The sensor was based on a QCM with an aptamer-based magnetic separation system for the rapid enrichment of target pathogens for on-line monitoring (Ozalp et al., 2015). More examples utilizing aptasensors for the detection of environmental pollutants, as well as additional information are presented in Table 4. Unfortunately, piezometric methods are characterized by low sensitivity and high detection limits in relation to other methods described.

Table 4. List of aptasensors used for different types of environmental pollution analytical purposes.

Type	Analytes	Aptamer based on …	Analytical method/transducer	LOD	Linear concentration range	Type of samples	References
Electrochemical sensors							
Polychlorinated biphenyls	PCB 77	DNA	DNA-aptamer-modified Au electrode modified with electroactive Fc	0.01 μg L^{-1}	0.2–200 μg L^{-1}	Environmental samples	Wu et al., 2016
		DNA	RGO-AuNP-Ap/Au Electrode	0.1 pg L^{-1}	0.001–10,000 nmol L^{-1}	Tap water	Wu, Lu, Fu, Wu, & Liu, 2017
Heavy metal	Cd^{2+}	DNA	AuNPs/CS modified GCE	0.05 pmol L^{-1}	0.001–100 nmol L^{-1}	Tap water	Liu, Lai, et al., 2017
Heavy metal	As^{3+}	DNA	SAM on SPCE via Au–S bond	0.15 nmol L^{-1}	0.2–100 nmol L^{-1}	Water samples	Cui, Wu, & Ju, 2016
Heavy metal	Hg^{2+}	DNA	DNA layer absorbent construct from nanocomposite of three-dimensional reduced GO and polyaniline	0.035 nmol L^{-1}	0.1–100 nmol L^{-1}	Aquarius solutions	Yang, Kang, et al., 2015
		DNA	Thymine-Hg^{2+}-thymine coordination chemistry and use of NPG for signal amplification	0.0036 nmol L^{-1}	0.01–5000 nmol L^{-1}	River and tap water, landfill leachate	Zeng et al., 2017
		DNA	Label-free based on the hybridization/dehybridization of double-stranded DNA on the Au electrode	0.6 zmol L^{-1}	5–55,000 zmol L^{-1}	Aqueous solutions	Amiri et al., 2017
EDCs	BPA	DNA	Nontarget-induced bridge assembly and aptamer extension reaction triggered by terminal deoxynucleotidyl transferase	15 pmol L^{-1}	0.08–15 nmol L^{-1}	Tap water and food samples	Abnous, Danesh, Ramezani, Alibolandi, & Taghdisi, 2018
		DNA	Photoelectrochemical AuNPs/ZnO	0.5 nmol L^{-1}	1–1000 nmol L^{-1}	Drinking water	Qiao et al., 2016
		DNA	CNTs/G powders are significantly impeded by their poor 3D conductivity	0.3 nmol L^{-1}	0.010–1000 μmol L^{-1}	Lake water	Wang, Wang, et al., 2015
Antibiotic	Tetracyclines	DNA	Reduced GO, magnetite (Fe_3O_4) and sodium alginate used to modify the surface of a screen-printed GCE	0.6 nmol L^{-1}	0.001–5 μmol L^{-1}	Water, food samples	Zhan et al., 2016
Antibiotic	Ofloxacin	DNA	AuNPs on the surface of GCE through sulfhydryl-terminated monolayer in which thiolated ssDNA probes are immobilized	1 nmo L^{-1}	50–20,000 nmol L^{-1}	Tap and waste water	Pilehvar et al., 2017.
EDCs/hormone	Progesterone	DNA	SAM/Au/$[Fe(CN)_6]^{3-/4-}$/EIS	900 ng L^{-1}	10–60 μg L^{-1}	Tap water, wastewater, groundwater	Contreras Jiménez et al., 2015
EDCs/hormone	17β-estradiol	DNA	Ni^{3+}, $Fe(CN)_6]^{3-}$/AuNP	0.8 pmol L^{-1}	1–60 pmol L^{-1}	Wastewater samples	Fan, Zhao, Shi, & Liu, 2015
		DNA	CoS/AuNPs	0.7 pmol L^{-1}	1–100 pmol L^{-1}	Water samples	Huang, Liu, Zhang, Cao, & Liu, 2015
Pesticide	Carbendazim	DNA	SAM thiol-modified aptamer on AuNPs electrodes	8.2 ng L^{-1}	0.01–10 μg L^{-1}	Environmental and food samples	Eissa & Zourob, 2017
Pesticide	Acetamiprid	DNA	PtNPs were deposited in a bridge-like arrangement, in	1 pmol L^{-1}	0.10–1 μmol L^{-1}	Water samples	Madianos, Tsekenis, Skotadis,
	Atrazine	DNA	between IDEs	10 pmol L^{-1}	0.010–100 nmol L^{-1}		Patsiouras, & Tsoukalas, 2018
Toxin	Cylindrosper-mopsin	DNA	TH–G nanocomposite through the cross-linker GA	0.117 μg L^{-1}	0.39–78 μg L^{-1}	Lake water	Zhao, Chen, Ma, Liu, & Wang, 2015
		DNA	Label-free impedimetric aptasensor (fluorescence assay aptamer on the Au surface)	100 pmol L^{-1}	0.1–80 nmol L^{-1}	Fresh water	Elshafey, Siaj, & Zourob, 2014
Toxin	Anatoxin-a	DNA	SAM formed on a Au electrode using the disulfide modified aptamer.	0.5 nmol L^{-1}	1–100 nmol L^{-1}.	Drinking water	Elshafey, Siaj, & Zourob, 2015
Toxin	Microcystin-LR	DNA	GCE|SDD–Co(II)|AgNPs	0.37 nmol L^{-1}	7.5–500 μmol L^{-1}	Water samples	Li, Cheng, et al., 2016
Plasticizer	Ethanolamine	DNA		0.08 nmol L^{-1}	0.16–16 nmol L^{-1}	Tap water	

			G-quadruplex-EA binding interaction is presented by using G-rich aptamer DNA and EIS				Liang, Man, Jin, Pan, & Liu, 2016
Optical sensors							
Polychlorinated biphenyl	PCB 77	DNA	AuNPs as a colorimetric probe	0.05 nmol L^{-1}	0.5–900 nmol L^{-1}	River and pound water	Cheng, Liu, Shi, & Zhao, 2018
Heavy metal	Pb^{2+}	DNA	Biosensor labeled with FAM	60.7 nmol L^{-1}	100–1000 nmol L^{-1}[a]	Serum and river water samples	Chen et al., 2018
		DNA	Label-free sensor with TH as the signaling molecule and GR as the signal-enhancing platform	0.032 pmol L^{-1}	0.16–160 pmol L^{-1}	Drinking, tap and lake water	Gao, Gao, He, Wang, & Wu, 2016
Heavy metal	Hg^{2+}	DNA	Aptamer-based fluorescence-quenching LFS	130 ng L^{-1}	130–4 000ng L^{-1}	River water	Wu, Shen, et al., 2017
			Fluorescence-labeled DNA containing T-T mismatch introduced to DNA probes immobilized onto the sensor surface	1.2 nmol L^{-1}	0–100 nmol L^{-1}	Lake water	Long, Zhu, Shi, Wang, & Liu, 2013
			Chemiluminescence biosensing platform with amplification mechanism from positively charged ((+)AuNPs)	16 pmol L^{-1}	620–1.2 μmol L^{-1}	Tap and river water	Qi, Xiu, Yu, Huang, & Li, 2017
Heavy metals	Cu^{2+}	DNA	Light-switchable (photocontrolled inclusion and exclusion responses of CD-containing surface conjugated with photoisomerizable azobenzene) monolayer self-assembly and host–guest interactions	1.5 μmol L^{-1}	1–14 μmol L^{-1}	Water samples	Wang, Wong, et al., 2015
EDCs/ Plasticizer	BPA	DNA	Aptamer based 'turn-off' fluorescent biosensor	0.1 μg L^{-1}	1–10,000 μg L^{-1}	Water samples	Ragavan, Selvakumar, & Thakur, 2013
		DNA	Aptasensor that uses a FRET mechanism. Water-soluble conjugated PFP is used as the energy donor and a FAM-labeled aptamer is used as the energy acceptor. Graphene oxide (GO)	5 ng L^{-1}	0–1.0 μg L^{-1}	Tap water	Guo, Hu, Zhang, & Tang, 2018
		DNA	FRET between fluorescein-labeled BPA aptamer and MGO	0.071 ng L^{-1}	0.2–10 ng L^{-1}	Tap, pure and river water samples	Hu et al., 2017
EDCs/ Plasticizer	BPA and BPS	DNA	Anti-BPA aptamer and the AuNPs as the output signal	1.5 μg L^{-1} for BPA1.3 μg L^{-1} for BPS	4.4–66 μg L^{-1} for BPA, 2.5–75 μg L^{-1} for BPS	Water samples	Zhang et al., 2017
		DNA	Wave fiber-optic aptasensor	1.86 nmol L^{-1}	2–100 nmol L^{-1}	Water samples	Yildirim et al., 2014
EDCs/hormone	17β-estradiol	DNA	Raman reporter molecule 4-mercaptobenzoic acid labeled Au-Ag core-shell nanoparticles and E2-aptamer endowed SERS	0.05 pmol L^{-1}	0. 001–10 nmol L^{-1}	Water samples	Liu, Cheng, Chen, Shi, & Zhao, 2018
		DNA	FRET for determination of 17β-estradiol.FAM-labeled E2 aptamer and its partially complementary DNA modified with BHQ1 formed aptamer/DNA duplexes with a competitive 'turn-on' aptasensor	100 ng L^{-1}	0.001–10 μg L^{-1}	Water and food samples	Zhang, Li, et al., 2018
		DNA	Smartphone imaging-based fluorescence microscopy using a microarray platform on a substrate with MEF using Ag film and Al_2O_3 nano-spacer	1 fg L^{-1}	1–100 fg L^{-1}	Wastewater samples	Lee et al., 2017

(*continued*)

Table 4. Continued.

Type	Analytes	Aptamer based on …	Analytical method/transducer	LOD	Linear concentration range	Type of samples	References
		DNA	AuNPs and Rhodamine B as sensing probe, fluorescent quencher and fluorescent indicator	0.48 nmol L^{-1}	0.48–200 nmol L^{-1}	Water samples	Ni et al., 2017
EDCs/hormone	Progesterone	DNA	Fluorescence detection[b]	110 pg L^{-1}	10–100 ng L^{-1}	Tap water	Alhadrami, Chinnappan, Eissa, Rahamn, & Zourob, 2017
Pesticide	Malathion	DNA	Cationic peptide and unmodified AuNPs	1.94 pmol L^{-1}	0.01–0.75 nmol L^{-1}	Environmental samples	Bala et al., 2017
Pesticide	Acetamiprid and Atrazine	DNA	Sputtering and e-beam lithography techniques, Pt NPs deposited in a bridge-like arrangement, in between IDEs	1 pmol L^{-1} for acetamiprid; 10 pmol L^{-1} for atrazine	0.10–100 nmol for acetamiprid; 0.1–1000 nmol L^{-1} for atrazine	Tap and mineral water	Madianos et al., 2018
Antibiotic	Oxytertra-cycline	DNA	GO hydrogel developed through a fast and facile gelation, immersion and fluorescence determination	25 μg L^{-1}	25–1000 μg L^{-1}	Environmental samples	Tan, Zhao, Du, Gan, & Quan, 2016
		DNA	Controllable peroxidase-like catalysis of a graphene/gold nanoparticle colorimetric aptasensor	91 nmol L^{-1}	0.17–0.50 μmol L^{-1}	Water samples	Yuan, Zhao, et al., 2017
Antibiotic	Sulfadimetho-xine	DNA	Label-free tunable peroxidase-like activity of G/Ni-Pd hybrids – colorimetric aptasensor	0.7 μg L^{-1}	1–500 μg L^{-1}	Lake water	Wang et al., 2017
Antibiotic	Ampicillin	DNA	AuNPs/MBs	70 ng L^{-1}	0.1–100 μg L^{-1}	River water	Luo et al., 2017
Piezoelectric sensors							
Heavy metal	Pb^{2+}	DNA	SAM of the AuNPs on the QCM	4 nmol L^{-1}	5–200 nmol L^{-1}	Water samples	Yuan, Song, et al., 2017
Toxin	Ochratotoxin A	DNA	EWA platform	3 nmol L^{-1}	6–500 nmol L^{-1}	Water and food samples	Wang, Xiang, Zhou, Liu, & Shi, 2015
Pathogen	*Salmonella enterica*	DNA	Aptamer-based QCM	—	100 CFU mL^{-1}	Water and food samples	Ozalp et al., 2015

3D, three dimension; AuNPs, gold nanoparticles; BHQ1, Black Hole Quencher 1; CD, α-cyclodextrin; CFU, colony forming unit; CoS, cobalt sulfide nanosheet; CNTs, carbon nanotubes; CTAB, cetyltrimethylammonium bromide; EDCs, endocrine disrupting compounds; EIS, Aptamer-based label-free impedimetric biosensor for detection of progesterone; EWA, evanescent wave all-fiber; FAM, 6-carboxyl fluorescein; FC, ferrocene; FRET, fluorescence resonance energy transfer; G, grapheme; GA, glutaraldehyde; GCE, glassy carbon electrode; GO, graphene oxide; IDEs, interdigitated electrodes; LFS, lateral flow strip; LOD, limit of detection; MBs, modified magnetic beads; MEF, metal-enhanced fluorescence; MGO, magnetic oxidation graphene; MIPMs, molecularly imprinted polymer microspheres; NPG, nanoporous gold; QCM, quartz crystal microbalance; PFP, poly(9,9-bis(6-N,N,N-trimethylammonium)hexyl)fluorine phenylene; PQC, piezoelectric quartz crystal; RGO, dotted reduction graphene oxide; RS, resonance scattering; SAM, self-assembled monolayer; SPCE, screen-printed carbon electrode; SERS, surface-enhanced Raman scattering; T, thymine; TH, thionine.

[a]Dissociation constants Kd = 1.60 ± 0.16 μmol L^{-1} and 0.76 ± 0.18 μmol L^{-1} (for two studied aptamers)

[b]Dissociation constant K_d = 2.1 nmol L^{-1}

3.2. Aptamer based tests

Aptamer-based assays may one day compete with the currently popular ELISAs (enzyme-linked immunosorbent assays) where antibodies are used as the recognition element. ELISAs are very sensitive and may be selective towards various analytes. However, antibodies are still required for ELISAs and as previously mentioned, antibody procurement requires an animal source. This factor may play a significant role in future preference for aptamer-based assays vs. ELISAs. Enzyme-linked apta-sorbent assays (ELASA) can be performed with different variations (enzyme-linked aptamer assay (ELAA), enzyme-linked oligonucleotide assay (ELONA) and aptamer-linked immobilized sorbent assay (ALISA)). Aptamers in these tests may be labeled with fluorescein and replaced with a secondary antibody, or they may directly bind the target molecule being attached to the medium and act as a primary antibody. Comparisons of ELONAs with ELISAs show that ELONAs are also a very sensitive and precise method (Shi et al., 2014; Toh et al., 2015). Aptatests are performed mainly on multi-welled test plates and the test endpoint is observed (by eye) or measured (by special equipment) by a change in color or fluorescence signal.

Aptamers may also serve as recognition elements in lateral flow assays (LFAs), which are a rapid format platform for the detection and quantification of analytes in complex mixtures. Currently, LFAs are usually used for home-based or *in situ* diagnostics, such as popular pregnancy tests; these tests are inexpensive, easy to use and utilize antibodies as a target recognition element (Koczula & Gallotta, 2016). Despite the effectiveness of antibody-based LFAs, alternative versions based on aptamers are sought after (Chen & Yang, 2015). The LFA strip/dipstick consists of several overlapping membranes that are mechanically stabilized on a small backing card, usually made from nitrocellulose. A few drops of sample are placed in the designated area, which then migrate laterally to the membranes at the conjugation pad by capillary force. There the fluid rehydrates a detection label composed of a recognition element (antibody or aptamer) coupled to a reporter molecule (AuNP), that form a complex with the target (Schüling, Eilers, Scheper, & Walter, 2018). The target molecule connects to the capturing molecule (AuNPs), and as soon as the complex target-AuNPs crosses the test line containing the aptamers or antibodies, the color of the strip can be observed by the naked eye. To assure proper test operation (proper fluid flow, activity of recognition, and capture molecules), there is also a control strip placed on the test strip. This type of design is known as a competitive design (Figure 9b) (Schüling et al., 2018). In a 'sandwich-LFA' (Figure 9a), when an analyte has multiple binding sites, the detection labels provided within the conjugation pad react with the target analyte to form a complex. This complex is then captured in the test strip by an interaction

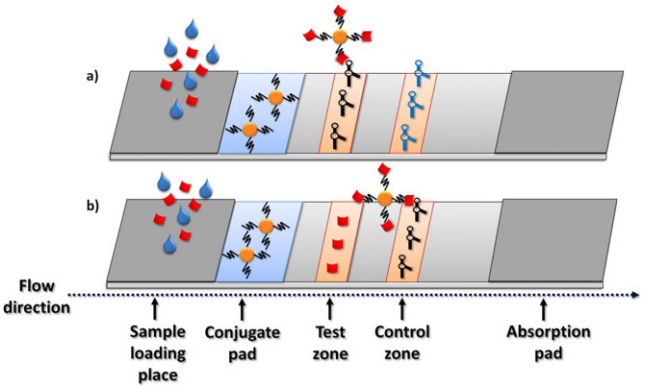

Figure 9. Sandwich LFA a) and competitive LFA with aptamer as recognition element (Bahadır & Sezgintürk, 2016; Jauset-Rubio, El-Shahawi, Bashammakh, Alyoubi, & O'Sullivan, 2017).

Table 5. Types of aptamer-based test and information about target molecules and lowest recorded concentration.

Test name	Aptamer type	Target/ Analytes	Samples	The lowest concentration of targets recorded in the research	References
ELASA	DNA	SGIV virus	Biological material	As low as 125 nmol L^{-1}	Li, Zhou, et al., 2016
	DNA	Basic fibroblast growth factor (bFGF)	Biological material	The minimum detection level of 7 pg mL^{-1}	Golden, Collins, Willis, & Koch, 2000
ELONA	RNA	Cytokines	Biological material	The minimum detection level was 100 pg mL^{-1}	Yan, Gao, Yao, & Zhang, 2004
	DNA	Zearalenone monoclonal antibody	Corn samples	—	Wang, Zou, et al., 2015
	DNA	*Leishmania infantum* H2A antigen	Biological material	—	Ramos et al., 2007
ALISA	DNA	Tulmeria antigen produced by *Francisella tularensis*	Bacterial cultures	Minimal concentration 100 ng mL^{-1}	Vivekananda & Kiel, 2006
ELAA	DNA	Influenza A virus	Virus breeding	—	Shiratori et al., 2014
LFSA	DNA	Hg^{2+}	Water samples	LOD – 0.13 ng mL^{-1}	Wu, Shen, et al., 2017
	DNA	Chloramphenicol	Food samples	LOD – 0.0031 ng mL^{-1}	Yan et al., 2018

LOD, limit of detection; LOQ, limit of quantification; ELONA, enzyme-linked oligonucleotide assay; ELAA, enzyme-linked aptamer assay; LFA, Lateral Flow Assay; ALISA, aptamer-linked immobilized sorbent assay.

between the analyte and the corresponding immobilized aptamers. The fluid reaching the test zone contains labeled and unlabeled target molecules that compete to bind to the capture molecules immobilized in the test zone. Examples of this along with additional information are presented in Table 5.

The use of sensors (in which the recognition elements are aptamers) makes the number of purposes to be determined becomes virtually

unlimited. Aptamers are small, chemically stable and cheaper compared to other sensors, in particular those based on antibodies. On the one hand, the ability to generate an aptamer to determine different targets is beneficial, but many of process of generating such aptamers are quite problematic. Aptasensors, in relation to other sensors, are characterized with high selectivity and sensitivity and the aptamers themselves are very stable molecules.

4. Other aptamer applications

4.1. Medical applications

Aptamers are considered 'smart ligands', which are ligands specially selected for specific parameters that generate a known biochemical reaction (Drabovich, Berezovski, Musheev, & Krylov, 2009). The aptamers most commonly used in medical applications focus on RNA bases that are more structurally diverse than DNA based aptamers. Known groups of aptamers can be directed to specific factors (A30, A9, A10, TTA1, and MUC1) located on the cytoplasmic membranes of tumor cells. These factors are extremely overexpressed only on the surface of tumor cell membranes (Pfeiffer & Mayer, 2016; Ferreira, Cheung, Missailidis, Bisland, & Gariepy, 2009; Zhou et al., 2016; Marton, Reyes-Darias, Sánchez-Luque, Romero-López, & Berzal-Herranz, 2010; Hicke et al., 2006). Aptamers used in targeted anticancer therapy are most often carriers of polymeric nanoparticles that contain antimitotic drugs such as paclitaxel; these medicines inhibit cancerous cell division (Dhar, Gu, Langer, Farokhzad, & Lippard, 2008; Tong, Yala, Fan, & Cheng, 2010).

In 2004, the FDA (Food and Drug Administration) approved Macugen® (pegaptanib), an aptamer based drug used to treat adults who suffer from wet-form age-related macular degeneration. In this treatment, a modified pegylated oligonucleotide binds selectively and strongly to the extracellular form of endothelial growth factor (VEGF165) to inhibit its action. In January 2017, the FDA approved oligonucleotide therapies following assessment that aptamer-based drugs provided a clear benefit in rigorously controlled clinical trials (Stein & Castanotto, 2017).

Radiology methods are used to identify, locate, and assess the degree of disturbance in the structure and function of examined organs. These methods require the use of contrast-friendly agents with a suitable signal for detection and high tissue specificity. Such a role may be played by labeled aptamers capable of binding to proteins found on the surface of specific tissues or cells. Using established *in vitro* tumor cell lines, aptamers directed against tenascin C (a marker protein produced in large quantities by cancer cells) and the extracellular domain of the RTK receptor (a tyrosine kinase

transmembrane protein involved in signal transmissions necessary for cancer proliferation and growth) have been successfully isolated (Hicke et al., 2001).

In addition to cancer cell detection, aptamers can be used to detect viruses, bacteria, and even parasites. There are reports of aptamers specific to the hepatitis C virus, influenza virus, type 1 human immunodeficiency virus, *Staphylococcus aureus*, *Bacillus subtilis*, and parasites that cause malaria. These aptamers bind to proteins present on the target membrane, or to host antibodies due to the presence of a given bacterium, virus, or parasite (Misono & Kumar, 2005; Biroccio, Hamm, Incitti, De Francesco, & Tomei, 2002; Pavski & Le, 2001; Someya et al., 2012; Cao et al., 2009).

Western blotting with aptamers instead of antibodies offers researchers multiple benefits including an increased number of fluorophores, which increase the signal-to-noise ratio, fewer nonspecific bands, direct conjugation to the reporter molecule, and lower costs. Aptameric Western blotting allows the selective staining of proteins transferred to a membrane and is more effective than antibodies. Although not common the using an RNA His-tag-specific aptamer (which was further conjugated to a QD) has been reported (Shin, Kim, Kang, Yang, & Hah, 2010; Radom et al., 2013). Aptamers are also currently used in imaging diagnostics as carriers of fluorescent dyes, such as fluorescein or rhodamine, which can be detected by spectroscopic techniques following activation (Xu, Yang, Ye, He, & Fang, 2006).

One of the very promising options for using aptamers is associated with point-of-care-testing (POCT) and personalized medicine of individual patients (Vashist, Luppa, Yeo, Ozcan, & Luong, 2015, Dhiman, Kalra, Bansal, Bruno, & Sharma, 2017). Among the many possibilities colometric and fluorescence tests offer the possibility of a quick visual assessment, which facilitates diagnostics and does not require specialist personel or equipment. The use of highly selective target binding aptamers enables fast color development that may be assessed qualitatively and/or quantitatively on simple spectrometer devices (Dhiman et al., 2017).

Three different generations of Point-Of-Care (POC) tests are especifically designed to work at different levels according to individual patient requirements. The first ones include maintenance-free rapid tests (e.g. LFAs), the second-generation cover cartridge-based tests (e.g. nucleic acidamplification tests), the third generation of aptamer-besed POC tests include personal hand-held equipments (Pai, Vadnais, Denkinger, Engel, & Pai, 2012, Dhiman et al., 2017). Aptamers are a promising tool in the POC test group, are easier to obtain than crosses, it is possible to introduce aptamers to the development of commercial technologies, some of the POC tests already described in the literature are summarized in Table 6.

4.2. Analytical applications

Although aptamers are increasingly applied in medical science, the possibilities for their use extend beyond the medical arena. Aptamers are used successfully in forensic science for toxicological analysis, to target analytes, and for chemical and biological weapons (Yáñez-Sedeño, Agüí, Villalonga, & Pingarrón, 2014). Aptamers can reveal latent fingermarks (Wood, Maynard, Spindler, Lennard, & Roux, 2012) and a deoxyribonucleotide-based aptamer is used to detect cocaine in body fluids (Stojanovic, De Prada, & Landry, 2001).

In affinity chromatography used for protein purification, specific aptamers are immobilized on a chromatography support to create an affinity column that separates the sample ingredients (Romig, Bell, & Drolet, 1999). Aptamer based electrochemical sensors have great potential due to their ability to recognize a large number of targets simultaneously present in environmental samples (Wu, Liu, Zhan, Wang, & Zhou, 2012; Hoang, Oyama, Saito, Aono, & Nagao, 2013; Li, Dong, & Wang, 2009; Hayat & Marty, 2014; Lee et al., 2009). Compared to aptamers, antibodies used in affinity chromatography have to be thoroughly purified before sample separation, lest the impurities significantly impact target isolation and purification. Additionally, there significant costs associated with obtaining antibodies and quality differences in the received batches.

4.3. Aptamer based tests

Aptamer-based tests can be used to detect food contaminants, for quality control, and as a diagnostic tool for early and rapid detection of specific risk factors (Toh et al., 2015). ELONA and ELAA tests are being developed to rapidly identify various pathogens including influenza viruses H1N1, HPV and the *Mycobacterium tuberculosis* (protein MPT64) bacteria (Bai et al., 2018; Sypabekova et al., 2017).

Recently Mukherjee, Manonmani, and Bhatt (2018) introduced ultrasensitive ELASA to detect aflatoxin B_1 at a detection limit of 10 pg mL^{-1} in a buffer. The aptamer based-test was characterized by higher sensitivity and recovery compared to antibody-based ELISA. Wu et al. (2015) described an LFA for the rapid visual assessment of the presence of *Escherichia coli* O157:H7 where as low as 10 CFU mL^{-1} could be detected in laboratory tests.

For the time being, biological tests with aptamers are not as developed as antibody-based analogs. However, as previously mentioned, aptamers are a good alternative due to their simple preparation methods and the wide environmental ranges in which aptamers are active. Figure 10 and Table 7

Table 6. POC aptamer-based tests and additional information about their use as well as advantages and disadvantages.

POC-tests (devices)	Analite	Type of sample	Limit of detection	Limitations	Advantages	Literature
Target-Responsive Hydrogel Pressure-Based Assay	Cocaine Ochratoxin A Pb^{2+}	Urine	Cocaine – 3.96 μmol L^{-1} Ochratoxin A – 37 nmol L^{-1} Pb^{2+} – 72 nmol L^{-1}	Need for a pressuremeter with excellent accuracy and selectivity	Simple sample processing, Good stability of PtNPs inside the hydrogel,	Liu, Jia, et al., 2017
Aptamer-based lateral flow assay	Cortisol	Sweat	1 nmol L^{-1}	Currently tests have a short shelf time	No need of external fluid pumping (due to capillary flow in the cellulose materials), low cost of materials, opera-tion with small sample volumes and without the need of skilled per-sonne	Dalirirad et al., 2019
Vancomycin (Van)-functionalized platinum nanoparticles (PtNPs@Van) and aptamer-coated magnetic $CuFe_2O_4$ nanoprobes	*S. aureus*	Milk and saliva	1.0 cfu/mL	Need for a pressuremeter with excellent accuracy and selectivity	Safe use, no need for experience personnel, environmentally friendly products and substrats	Li et al., 2019
(PEDOT-OH:TsO) microelectrode array	Influenza A	Saliva	—	Cleaning and re-usability of the sensor is questionable	Highly sensitive, highly specific, highly stable, and has a very competitive response time	Kiilerich-Pedersen, Daprà, Cherré, & Rozlosnik, 2013
Colometric assay	Streptomycin	Biological material (chicken and milk)	94 nmol L^{-1}	Possibility of color variation	Good selectivity, simple operation and on-site visualization (on simple device such as smartphone)	Lin et al., 2018

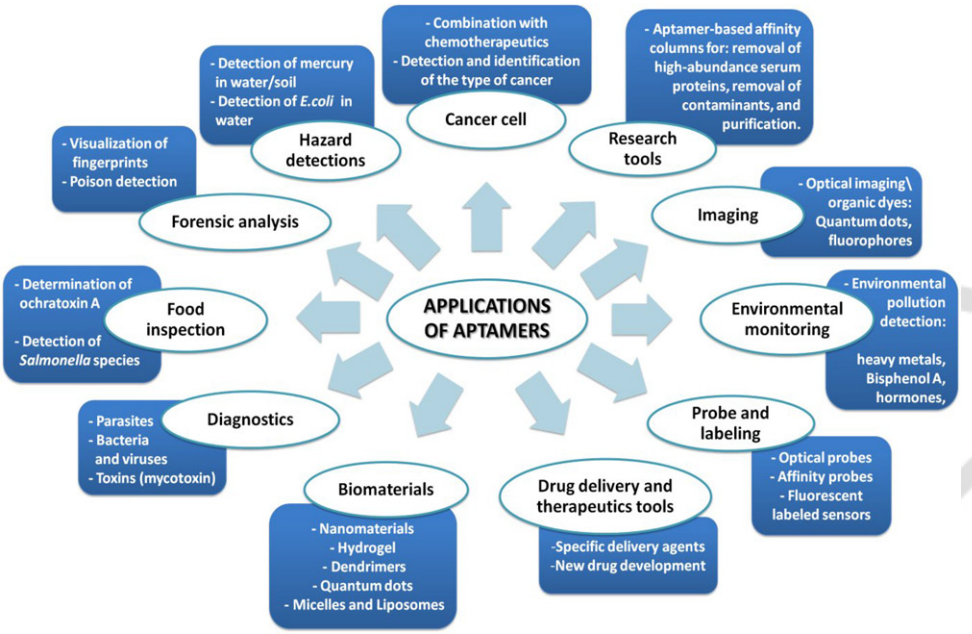

Figure 10. Applications of aptamers (Keefe, Pai, & Ellington, 2010; Daniel, Mélaïne, Roupioz, Livache, & Buhot, 2013; Hicke et al., 2006. Wiedman et al., 2017; Pfeiffer & Mayer, 2016; Jin et al., 2016; Battig & Wang, 2014; Darmostuk, Rimpelova, Gbelcova, & Ruml, 2015; Cruz-Aguado & Penner, 2008; Joshi et al., 2009; Hayat & Marty, 2014; Bagalkot et al., 2007; Wood et al., 2012. Song, Jurng, Park, & Kim, 2016).

contain a summary of the different applications of aptamers in various scientific fields.

5. Future perspectives

The emergence of artificial genetic polymers known as xeno nucleic acids (XNAs) offer several options for the creation and synthesis of polymers that function like DNA and RNA. However, XNAs are poorly recognized by organism nucleases, making them highly resistant to decay and resulting in longer half-lives *in vivo*. Modifications to the XNA backbone include sugar replacements, such as those in locked nucleic acids, arabinonucleic acids, cyclohexenyl nucleic acids, 1,5-anhydrohexitol nucleic acids, and 2′-fluoroarabinonucleic acids (Bruno, 2015; Østergaard et al., 2014; Istrate, Medvecky, & Leumann, 2015). XNAs can be used to develop ultra-stable aptamers, however, any such modification may increase the risk of an adverse patient reaction (Bruno, 2015).

Aptamers also demonstrate the potential for stem cell differentiation, possibility indicating the ability to replace expensive recombinant growth factors in regenerative medicine, or to discover unknown surface cell receptors (Bruno, 2017). Stem cell differentiation can be beneficial in targeted

Table 7. Examples of applications and additional information of aptamers in various fields of science.

Target/analyte	Features/Aptamer function	Type of samples/active sites	Comments	Reference
Cocaine	Electrochemical sensors	Human blood serum	LOD – 100 pmol L^{-1}	Roushani & Shahdost-fard, 2015
	Piezoelectric sensors	Biological material	LOD – 0.9 μmol L^{-1}	Neves, Blaszykowski, Bokhari, & Thompson, 2015
Oxytetracycline	ELAA	Milk samples	2.3 μg L^{-1}	Kim, Lee, Min, Lim, & Jeong, 2014
		Food samples	LOD 0.88 ng mL^{-1}	Lu, Tang, Liu, Kang, & Sun, 2015
Tetracycline	ELASA	Bovine milk	DNA – 15.7 mg L^{-1}, RNA – 10.1 mg L^{-1}	Toh et al., 2015; Jeong & Rhee Paeng, 2012
Hg^{2+}	Turn-on fluorescence bioassay	Food samples	LOD – 60 nmol L^{-1}	Liu, Ouyang, et al., 2018
	FI CV AAS	Biological material	LOD – 0.05 μg L^{-1}	Farzin, Shamsipur, & Tabrizi, 2015
Pb^{2+}	ICP-MS	Biological sample	LOD 0.05 μgL^{-1}, range 0.3–867.5 μg L^{-1}	Shamsipur, Farzin, Amouzadeh Tabrizi, & Sheibani, 2017
Dopamine	ELAA	Serum	no data	Park & Paeng, 2011
Vaspin	LFA	Serum and buffer samples	Detectable concentrations up to 5 nmol L^{-1}	Raston, Nguyen, & Gu, 2017
Purification of antibiotics	Affinity-based chromatography	Pure substances/solutions	—	Yang et al., 2017
Cancer markers	Piezoelectric sensors	Biological samples	High sensitivity (250 ng L^{-1}), fast detection (within 30 min) with small samples (1 μl)	Su, Fong, Cheung, & Yang, 2017
Drug carrier for doxorubicin in cancer therapy	RNA	Cancer tissue	—	Zhuang et al., 2016
HIV-1 Tat protein	Piezoelectric sensor	Human blood serum	—	Tombelli, Minunni, Luzi, & Mascini, 2005
Hepatitis C virus Envelop protein E2	Diagnostic tool	Biological fluids	—	Chen, Chen, Zhou, Chen, & Chen, 2015
H1N1 virus	Electrochemical sensors	Biological fluids	LOD – 0.3 ng μL^{-1}	Bai et al., 2018
	ELONA		LOD – 0.9 pg μL^{-1}	
HPV	LFS	Biological fluids	–	Liu, Zhang, Liu, Sharma, & Ding, 2017
Leukocyte cell adhesion molecule	ELAA	Blood samples	Lowest detected concentration 0.31 ng mL^{-1}	Her, Jo, & Ban, 2017
Listeria monocytogenes	ELONA	Food	—	Liu, Lian, et al., 2014
Escherichia coli	LFA	Food samples	min. 10 CFU mL^{-1}	Wu et al., 2015
Salmonella enteritidis	BI-3000 plasma resonance biosensor	Food samples	LOD – 2 CFU mL^{-1}	Di, Du, Pan, & Wang, 2017
Staphylococcus aureus enterotoxin C1	Fluorescent bioassay	Food samples	LOD – 6 ng mL^{-1}	Huang, Chen, et al., 2015
Mycobacterium tuberculosis secre-ted protein MPT64	ELONA	Clinical sputum samples	—	Sypabekova et al., 2017
Ochratoxin A	Electrochemical sensor	Food samples	—	Somerson & Plaxco, 2018
	ALISA	Beer	LOD and the LOQ are 0.82 and 2.5 mg L^{-1}	Costantini et al., 2016
	ELASA	Wine	Limit of detection 1ng mL^{-1}	Barthelmebs, Jonca, Hayat, Prieto-Simon, & Marty, 2011
Cholera toxin	ELAA	Tap water	2.4 ng mL^{-1}	Frohnmeyer, Frisch, Falke, Betzel, & Fischer, 2018

LOD, limit of detection; LOQ, limit of quantification; ELONA, enzyme-linked oligonucleotide assay; ELAA, enzyme-linked aptamer assay; LFA, Lateral Flow Assay; FI CV AAS, Flow Injection Cold Vapor Atomic Absorption Spectrometry.

cancer therapy (Shamaileh et al., 2016). Aptamers have also proved to be promising biorecognition elements in the development of electrochemical-based sensors. Aptameric identification capabilities with selective detection capacities for electrochemical signal transduction enable an almost unlimited number of biosensors. Unfortunately, the currently limited number of proven aptamers hinders the progression of aptamer-based electrochemical sensor development (Liu, Morris, Macazo, Schoukroun-Barnes, & White, 2014).

Due to their small sizes and dimensions, aptamers may cross physiological barriers, enabling the delivery of therapeutic and diagnostic agents to intracellular organelles. Targeted/tailored nano-delivery will allow cell-based strategies for delivery of active substances to the mitochondria, nucleus, lysosomes, or endoplasmic reticulum. However, it is important to understand the basics of organelle-targeted drug delivery strategies, which are critical to the design and successful use of biomedical nanomaterials for therapeutic treatment (Ma, Gong, Zhong, Sun, & Liang, 2016). The combination of liposomes and aptamers is characterized by high efficacy and selectivity in the treatment of many diseases, including many types of cancer. In addition, aptamer-liposome combinations can be used as highly selective diagnostic sensors (Ries & Vogel, 2016).

It is very likely that aptamers will replace antibodies in certain scientific and medical areas in the future (Li, Ho, & Ding, 2015). Research on aptamers continues to increase, and the PubMed publication database contains almost 8,000 articles on this subject (PubChem, 2018). In terms of environmental monitoring, aptamer potential is not yet fully utilized. Aptamer based biosensors or tests for the presence of environmental pollutants are still primarily in the prototype phase of development and are usually tested on samples with simple matrices such as tap or ground water. However, current reports are very promising, especially regarding the ability of aptamers to recognize a wide range of analytes at very low levels, in addition to the possibility of regeneration and their considerable stability (Justino et al., 2017; Verna and Bhardwaj, 2015).

Based on a review of the current data, one can conclude that the utilization of aptamers in the 21st century is limited only by their intrinsic properties and the imagination and skills of the researcher. Environmental protection and monitoring issues are of growing importance in developed, developing and underdeveloped countries, so intelligent solutions for rapid diagnostic measurements *in situ* are required. The ease of preparing arrays for quick-format biotests and detection systems makes aptameric testing a promising solution in the following nine areas:

1. Aptamers can be used for designing rapid-format tests and portable analyzers for environmental monitoring and pollutant screening. This

includes mixtures and samples characterized by complex matrix effects (Hsieh, Dantzler, & Weigl, 2017) and the automated assessment of risk/exposure to different organisms based on advanced big-data treatments growing more accessible to an increasing number of societies (Ali et al., 2016; Andreu-Perez, Poon, Merrifield, Wong, & Yang, 2015; Bellinger, Jabbar, Zaïane, & Osornio-Vargas, 2017; Lokers, Knapen, Janssen, van Randen, & Jansen, 2016; Romero, Hallett, & Jude, 2017).

2. Aptamers can be used for performing quick and comprehensive certified patient diagnostics at the point-of-care (or even at an accident site) to facilitate the process of decision making and the undertaking of life-saving actions (Burbelo, Ramanathan, Klion, Iadarola, & Nutman, 2008; Hesterberg & Crosby, 1996). Certain decisions on e.g. patients TRIAGE (French: to segregate) in cases of poisoning with unknown substances (or their mixtures, e.g. boosters), infection with unknown rare bacteria/viruses, detection of possible allergic reaction to some pharmaceuticals of first choice (e.g. anesthetics) or showing symptoms of unknown biochemical disorders can be undertaken already at first glance with basic-level medical personnel to facilitate efficiency of patients care and shortening, afterwards, recovery time. Rapid development in this area of science justifies conclusion that it is worth to prepare separate scientific review paper on this topic of interest.
3. Aptamers can be used as a certified early-warning system in households or public institutions (e.g. schools, hospitals) to rapidly detect the malfunction of media delivering systems, or even accidents or attacks with unknown agents that pose a threat to exposed individuals (Collins & Kapucu, 2008; Macherera & Chimbari, 2016; Moffitt et al., 2011; Greenhalgh, Robert, Macfarlane, Bate, & Kyriakidou, 2004).
4. Aptamers can be used to create tailored 3D printed closed-loop modules that combine aptamers with bioassays (and possibly instrumental detection systems) to conduct chronic exposure studies of single and combined pollutants in organisms from different trophic levels (Juraschek, Cerdas, Posselt, & Herrmann, 2017; Debski et al., 2018; Fang et al., 2017).
5. Aptamers can be used for rapid screening for boosters or illegal products in patient or convict body fluids for first-aid units or police or border guards (Avtonomov & Kornienko, 2015; Bendahan, 2017).
6. Anti-terror aptasensor arrays can be used for detecting attacks with nerve gases, explosives, and biological or chemical agents. These sensors could also identify the transport of these agents, which is currently a challenging task. This is especially true when dealing with air samples that need to be studied and treated, while simultaneously detecting active agents to undertake protective actions if required (Caygill, Davis, & Higson, 2012; Ma, Wang, & Wang, 2015; Wells & Bradley, 2012).

7. Aptamers can be used for food safety and packaging material stability research after elaborating universal and package oriented methodologies based on international standards (Szczepańska, Kudłak, & Namieśnik, 2018).
8. They can be used to screen for doping incidences in human or animals sports (Alvarez-Risco, Del-Aguila-Arcentales, Delgado-Zegarra, Yáñez, & Diaz-Risco, 2019; Ayotte, Miller, & Thevis, 2017; Thevis, Kuuranne, Geyer, & Schänzer, 2017). In case of consumers point of view, the application of aptamers may be helpful in authentication of food products by performing cheap rapid-format aptasensors-based quickly read-out by consumers themselves (or quality control personnel).
9. Target oriented aptasensor arrays can be used for screening the restoration/remediation process efficiency (Bardos et al., 2015; Sevcu et al., 2017). Automated read-out can be even performed by unskilled patients themselves or non-skilled personnel by taking photo (with smart- or wearable devices) of quick-assay result and transferring data to cloud; certainly, based on current developments in the field, results interpretation can be easily done either automatically or by professionals for initial screening of any above mentioned applications or to observe progress of ongoing processes e.g. of medical treatment at non-hospital conditions. More and more tests can be analyzed using generally available devices such as a camera, scanner or smatrphone. Due to the possibility of taking good quality photos and various image processing software and portability, one of the best smartphones is considered image acquisition tools. Literature provides examples of the use of aptamer-based tests that can be analyzed with the use of a smratphone e.g. in 2019 Umrao et al. propose a FRET aptasensor with dye pairs on DNA aptamers to rapid and sensitive kanamycin detection, which reached the limit of detections of 28 nmol L^{-1} (Umrao, Anusha, Jain, Chakraborty, & Roy, 2019).

Additionally, technological development will contribute to the rapid production of highly selective aptamers and a reduction of their cost, which is smaller than that of antibodies but still significant (Song, Zhang, Zhu, & Yang, 2015). The rapid development of artificial intelligence (AI), especially in terms of data interpretation and big data mining, as well as the potential application in designing/tailoring aptamers and correlating results with individual patients should also be considered.

6. Conclusions

i. Aptamers have unique intrinsic properties, manifesting in the specificity and selectivity of the interactions between aptamers and target

molecules. These properties affect aptameric aptitude for therapeutic utilization, and environmental pollutant analyses.

ii. The widespread use of aptamers depends on conditions including the cost, development of specific aptamers, and incorporation with other available technologies. All of these tasks are challenging but achievable, assuming rational cooperation between scientists including biologists, chemists, biotechnologists, chemometricians, toxicologists, and doctors, as well as stakeholders, authorities (and their social representatives), and NGOs.

iii. The review provides an overview of the current technologies and methodologies for the creation and utilization of aptamers with a specific focus on environmental and medical fields. The development of a variety of applications and methods of utilizing aptamers are thoroughly discussed and for these reasons would interest readers in the fields of biosensors, medicine, or environmental monitoring; it makes a significant contribution to the literature by consolidating existing data on aptamers. This makes it possible to clearly see overlapping applications for this technology as well as the potential for cross-disciplinary collaboration.

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