Discover Chemistry

Review

Aptamers and antibodies in optical biosensing

Kelvin Mpofu[1] · Sipho Chauke[1,2] · Lungile Thwala[1] · Patience Mthunzi-Kufa[1,2,3]

Received: 13 August 2024 / Accepted: 7 February 2025
Published online: 24 February 2025
© The Author(s) 2025 OPEN

Abstract

Optical biosensing has emerged as a vital tool for real-time, sensitive detection of biological analytes, with aptamers and antibodies leading as key molecular recognition elements. This review examines and compares their distinct roles, advantages, and limitations in optical biosensing. Antibodies, celebrated for their high specificity and mature production protocols, are often preferred in clinical diagnostics. However, challenges like cross-reactivity, environmental sensitivity, and production costs prompt exploration of alternative biorecognition molecules. Aptamers, nucleic acid–based recognition elements, offer several unique advantages, such as ease of synthesis, chemical stability, and amenability to modifications for improved target binding. While their relatively recent discovery means fewer standardized protocols and clinical applications compared to antibodies, aptamers show promise in complex sample matrices and emerging sensor platforms. This review also explores technological advances in both aptamer and antibody integration, surface modification strategies to enhance binding specificity and orientation, and regeneration methods to ensure biosensor reusability. Through a comprehensive comparison, the article aims to identify scenarios where one molecular recognition element holds distinct advantages over the other, paving the way for strategic applications in diagnostics, food safety, and environmental monitoring. In this review, we have explored the advancements and challenges associated with optical biosensing technologies, with a particular focus on LSPR-based sensors. Recent developments in nanoparticle fabrication, hybrid sensor platforms, and external stimulus-responsive systems have opened new avenues for biosensing applications in clinical diagnostics, environmental monitoring, and food safety. The review also discussed the integration of optical biosensors with Raman spectroscopy for enhanced analytical capabilities and highlighted innovations in metamaterial-based sensors for improved sensitivity and specificity. Despite these advances, several challenges remain, including surface stability, reproducibility, and limitations in detecting low-abundance analytes. Addressing these challenges will require further improvements in device design, bioreceptor immobilization strategies, and signal enhancement techniques. Future research efforts should also focus on the development of portable and cost-effective biosensing platforms that can be applied in resource-limited settings. Ultimately, this review provides valuable insights into future trends in aptamer and antibody-based biosensors, encouraging cross-disciplinary collaboration and innovation.

Keywords Aptamers · Antibodies · Optical · Biosensing · Plasmonics

Kelvin Mpofu, Sipho Chauke, Lungile Thwala and Patience Mthunzi-Kufa have contributed equally to this work.

✉ Kelvin Mpofu, KMpofu@csir.co.za; Sipho Chauke, schauke@csir.co.za; Lungile Thwala, lthwala@csir.co.za; Patience Mthunzi-Kufa, PMthunziKufa@csir.co.za | [1]Biophotonics, Photonic Centre, Manufacturing, Council of Scientific and Industrial Research (CSIR), Pretoria, South Africa. [2]Molecular and Cell Biology Department, University of Cape Town, Cape Town 7701, South Africa. [3]School of Interdisciplinary Research and Graduate Studies (UNESCO), College of Graduate Studies, University of South Africa, Preller Street, Muckleneuk Ridge, Pretoria, South Africa.

Abbreviations

ssDNA	Single-stranded Deoxyribonucleic acid
RNA	Ribonucleic acid
SELEX	Systematic evolution of ligands by exponential enrichment
kDa	Kilo Daltons
nm	Nanometers
POC	Point-of-care
SPR	Surface plasmon resoance
LSPR	Localised surface plasmon resonance
RT-LAMP	Reverse-transcription loop-mediated isothermal amplification
COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
PDMS	Polydimethylsiloxane
LOD	Limit of detection
SERS	Surface-enhanced Raman scattering
NA	Nucleic acid
DNA	Deoxyribonucleic acid
NPs	Nanoparticles
AuNPs	Gold nanoparticles
MNPs	Magnetic nanoparticles
ELISA	Enzyme-Linked Immunosorbent Assay
HIV	Human Immunodeficiency Virus
LFIA	Lateral flow immunoassay
FRET	Förster Resonance Energy Transfer
FLIM	Fluorescence Lifetime Imaging Microscopy

1 Introduction

The recent global health crises, marked by the emergence and re-emergence of pandemics and epidemics, underscores the urgent need for advanced diagnostic tools [1]. Enhanced biosensors are essential for the timely identification and control of infectious illnesses, which can spread rapidly and have devastating impacts on public health and economies [2]. These devices enable timely identification of pathogens at very low concentrations, often before symptoms manifest, significantly improving response times and enabling effective containment measures. Enhanced biosensor technology can also facilitate ongoing monitoring of disease spread and mutation, providing critical data to guide public health decisions and vaccine development. The development of highly sensitive biosensors is not just a technological advancement; it is a vital component in strengthening global health security against current and future biological threats [3–7]. Biosensors are analytical devices that combine a biological component with a physicochemical detector to measure a chemical substance, often at very low concentrations. These devices are crucial in various applications, including medical diagnostics, environmental monitoring, food safety, and biotechnology. Biological elements, such as enzymes, antibodies, or nucleic acids, specifically interact with the target analyte. The system of the sensor then detects and processes a signal that is proportional to the substance's concentration. The integration of biological sensing elements with electronic systems has led to the development of highly sensitive and selective biosensors that provide rapid, real-time, and often portable means of analysis. The field of biosensors continues to expand, driven by advances in biotechnology, nanotechnology, and material science, paving the way for innovative applications that address complex analytical challenges across various industries [8].

Biosensing technologies have become crucial in various fields, including healthcare, environmental monitoring, and food safety. Among the available techniques, optical biosensors have emerged as a transformative tool due to their ability to provide rapid, sensitive, and label-free detection. Unlike traditional methods such as electrochemical sensing and chromatographic techniques, optical biosensors leverage light-matter interactions to detect molecular changes in real-time, making them ideal for applications that require both precision and speed. The growing interest in optical biosensing can be attributed to several distinct advantages. First, these sensors offer high specificity and sensitivity by exploiting techniques such as Surface Plasmon Resonance (SPR), Localized Surface Plasmon Resonance

(LSPR), and photonic crystals. These methods are capable of detecting analytes at concentrations as low as femtomolar levels, surpassing the detection limits of many conventional techniques [9]. Second, optical biosensors can operate in a label-free manner, reducing the need for complex sample preparation and costly reagents. This feature makes them particularly attractive for applications in clinical diagnostics and point-of-care testing [10]. In addition to their sensitivity, optical biosensors are compatible with a wide range of bioreceptors, including antibodies, aptamers, and DNA probes. The versatility of these sensors allows for the detection of various biomolecules, ranging from proteins and nucleic acids to small metabolites, making them highly adaptable for multiple applications. Furthermore, the miniaturization of optical biosensing platforms, such as integrated photonic circuits, offers a pathway towards portable and cost-effective devices suitable for field use [11]. Despite these advantages, the successful implementation of optical biosensors depends on several key factors. Sensitivity, specificity, stability, and reproducibility are critical parameters that must be optimized for practical applications. Additionally, the development of robust device platforms and efficient surface functionalization strategies is essential to achieve reliable biosensing performance. These challenges have driven significant research efforts towards improving optical biosensor design and fabrication techniques. Compared to other methods, such as electrochemical and fluorescent-based sensing, optical biosensors stand out due to their ability to detect changes without direct electrical contact or the need for chemical labels. This makes them particularly useful in sensitive environments where the integrity of the sample must be preserved, such as in biological fluids or live-cell imaging [11]. Furthermore, advancements in metamaterial-based and hybrid biosensing platforms have opened new avenues for multiplexed detection and enhanced signal modulation, paving the way for innovative diagnostic tools. In this review, we explore the developments in optical biosensing technologies, focusing on their design, applications, and future directions. We aim to highlight the key advancements in nanoparticle fabrication, device integration, and signal modulation that have enabled new possibilities in biosensing. The challenges and opportunities associated with these technologies will be discussed in detail, with an emphasis on the emerging trends such as hybrid LSPR-fluorescence systems and external stimulus-responsive sensors.

In the evolving landscape of biomedical research and diagnostic technology, optical biosensing has emerged as a pivotal technique, offering good precision and sensitivity in diagnostic applications. This approach capitalizes on the unique properties of light to detect and quantify biological entities, revolutionizing the way we approach the diagnosis and monitoring of various health conditions. Optical biosensors also have the added advantage of being label-free, offering real-time detection, and being relatively easy to operate. These optical biosensors, however, do come with some challenges relating to binding specificity, bioreceptor properties, biosensor array design, and low-volume high-sensitivity challenges [12].

Specific Binding: The ability of biosensors to identify target analytes accurately is crucial, particularly when other chemicals, molecules, or cells are present in the sample [13]. This task becomes particularly complex in samples with diverse components. For instance, accurately detecting a specific antibody in a blood sample requires disregarding the influence of other antibodies, cells, and electrolytes to ensure the results truly reflect only the targeted antibody's concentration. Similarly, identifying a specific heavy metal ion in contaminated water demands distinguishing the ion's specific reactions amidst various other ions. Non-specific Binding: Also known as biofouling, this phenomenon often causes significant noise, signal drift, or delays in biosensors [14]. One common strategy to mitigate non-specific binding is thoroughly washing the sensor's surface with a buffer solution after the binding process to minimize unwanted interactions. Bioreceptor Properties: Research shows varying results concerning the concentration and arrangement of bioreceptors on sensor surfaces [15]. Protocols for surface activation, modification, and functionalization are critical but highly dependent on specific operational and environmental conditions. Variations in the immobilization of bioreceptor layers, such as those used on stable surfaces like gold and silicon, can affect the repeatability of measurements. Rarely do studies analyze the impact of bioreceptor alignment on biosensor performance, yet the random orientation of linking molecules can reduce effectiveness and sensitivity. Chu suggested a method to align chemical linkers on nanowire-based sensors by applying an external voltage, enhancing detection sensitivity significantly through prolonged molecular orientation [16]. Biosensor Assay Design: Schneider's research highlights how specific and non-specific bindings influence sensor signals and underscores the necessity of optimized sensor assay designs, particularly in complex samples [17]. This includes integrating proper reference sites to counteract non-specific bindings. Enhancements in both the imaging and data processing capabilities of biosensors are required due to the increased complexity of surface treatment and the varied optical properties of bioreceptors [12]. Low-Volume High-Sensitivity Challenges: In point-of-care (POC) and lab-on-a-chip (LOC) technologies, a small blood sample from a finger prick can contain tens of thousands of biomarkers at extremely low concentrations, presenting significant detection challenges due to the limited number of target molecules available [12].

A significant amount of research is currently underway to mitigate or eliminate some of the challenges associated with optical biosensors [12]. One particular solution is to consider the use of aptamers as opposed to antibodies, which are typically used for disease detection in diagnostic applications. As such, this work reviews the use of antibodies and aptamers on optical biosensors and presents a comparison of technologies with the aim of eventually developing better diagnostic technologies. In this context, better refers to improved sensitivity and, by extension, a lower limit of detection as well as improved performance. At the heart of this work are the technological advancements due to two key components: aptamers [18–24] and antibodies [25–32].

Aptamers, often described as chemical antibodies, are short, single-stranded DNA or RNA moleculess [22–24]. Their ability to fold into diverse three-dimensional structures enables them to bind specifically and tightly to a wide range of target molecules, including proteins, small molecules, and even cells. This specific binding is critical in the optical biosensing domain, where the detection of minute changes in biological samples can be pivotal. Antibodies, on the other hand, are naturally occurring proteins that play a vital role in the immune system [18, 19, 23, 24]. They can specifically recognize and bind to antigens, making them indispensable tools in biosensing applications. The use of antibodies in optical biosensing leverages their inherent specificity and affinity for target molecules, allowing for highly selective and sensitive detection. They are synthesized through a process known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX). These molecules are unique in their ability to fold into complex three-dimensional structures. Aptamers bind to their targets with high specificity and affinity. This is due to their three-dimensional structures, which allow them to fit snugly into the target molecule, much like a key fits into a lock. They can bind to a wide range of targets, including proteins, small molecules, ions, and even whole cells [20–24]. Aptamers offer several advantages over traditional biorecognition elements. They are easy and cost-effective to synthesize and can be modified to enhance their stability and binding properties. Additionally, aptamers do not elicit an immune response, making them suitable for therapeutic and diagnostic applications. In biosensing, aptamers are used for the specific recognition of targets, enabling the detection and quantification of various biomarkers [22–24]. They are also employed in drug delivery systems and as therapeutic agents.

Antibodies, on the other hand, are naturally occurring proteins that play a vital role in the immune system [25–28]. They can specifically recognize and bind to antigens, making them indispensable tools in biosensing applications. The use of antibodies in optical biosensing leverages their inherent specificity and affinity for target molecules, allowing for highly selective and sensitive detection. The integration of aptamers and antibodies in optical biosensing systems has led to the development of a wide array of diagnostic tools. These range from simple handheld devices for point-of-care testing to sophisticated laboratory equipment capable of detecting and quantifying biomarkers at extremely low concentrations. The impact of these advancements is far-reaching, offering promising implications for early disease detection, real-time monitoring of disease progression, and personalized medicine. Antibodies, also known as immunoglobulins, are large, Y-shaped proteins produced by the immune system. They consist of two heavy and two light chains, forming a structure that allows them to bind specifically to antigens [26–28]. Antibodies recognize and bind to specific antigens through the variable regions at the tips of their "Y" structure. This binding is highly specific, enabling antibodies to target specific pathogens, cells, or molecules. The high specificity and affinity of antibodies make them ideal for use in diagnostic assays, therapeutic applications, and research. They can be produced in large quantities through biotechnological methods and can be modified for various applications. Antibodies are widely used in diagnostic tests, including ELISA (Enzyme-Linked Immunosorbent Assay) and immunohistochemistry. They are also fundamental in therapeutic applications, such as in the development of monoclonal antibody drugs, and are key tools in biomedical research.

A crucial parameter for assessing biosensor performance is the limit of detection (LOD). The LOD represents the smallest detectable change in a parameter of interest, x, which in optical experiments can be the wavelength, refractive index, phase, or incident angle. For a measured signal y, the LOD in optical biosensors is dependent on the noise of the transduction signal, which determines the smallest resolvable signal, and the sensitivity, $\mathcal{S}$ [33]. Researchers can enhance the LOD by either improving the sensitivity or reducing noise. However, inherent statistical fluctuations in the light (shot noise) limit sensitivity improvements. This noise sets a fundamental limit known as the shot-noise limit (SNL) [33]. The sensitivity in optical biosensors depends on changes in the refractive index due to the analyte binding, leading to shifts in the measurable signal via precise detection. However, detection precision is ultimately constrained by shot noise. Studies have shown that leveraging quantum states of light (such as NOON, squeezed, or Fock states) can minimize measurement noise, improving the LOD below the classical SNL limit [33–37]. The sensitivity $\mathcal{S}$ of the biosensor is given by:

$$\mathcal{S} = \left|\frac{\partial y}{\partial p}\right|, \quad (1)$$

where p is the parameter estimated from the signal y. The sensitivity of the biosensor is also a funtion of the antigen used, i.e, it can be improved by using aptamers over antibodies. To compare different optical sensors' performance in detecting the refractive index, the LOD formula. The LOD refers to the smallest concentration of an analyte that can be reliably distinguished from the absence of the analyte, typically defined as three times the standard deviation (σ) of the mean signal in a control sample:

$$\text{LOD} = 3 \times \frac{\sigma}{m} \quad (2)$$

where σ is the standard deviation of the blank or control measurement, and m is the slope of the calibration curve, often referred to as the sensitivity [38]. Sensitivity is also defined as the slope of the calibration curve (m) that relates the analytical signal (e.g., absorbance or intensity) to the concentration of the analyte. It reflects how much the signal changes in response to a unit change in analyte concentration. This distinction is essential, as LOD assesses the system's detection capability at very low concentrations, while sensitivity describes the system's response across a range of concentrations. Thus, while sensitivity contributes to determining the LOD, they are distinct parameters with different implications in biosensing applications. For further information on the proper use and definition of LOD and sensitivity, refer to the work by Acunzo et al. [38].

In this paper, we discuss the fundamentals of optical biosensing, investigating the distinct characteristics of aptamers and antibodies that enhance the specificity and sensitivity of these methods. We will also examine the latest advances in the field and highlight how they shape the future of diagnostics and patient care. This work, will further explore various rapid, accurate, specific, and sensitive optical nanobiosensor-based diagnostic tools for detecting pathogens (Fig. 1).

2 Aptamers and antibodies

2.1 Comparison

Antibodies, also known as immunoglobulins, are large, Y-shaped proteins produced by the immune system (Fig. 2). Antibodies are proteins that play a role in adaptive immunity (mainly in vertebrates) by targeting antigens often produced in response to pathogenic microorganisms [40–42]. Antibodies consist of light and heavy chains (also known as moieties) that are bound together by disulfide bonds, forming a structure that allows them to bind specifically to antigens [42–46].

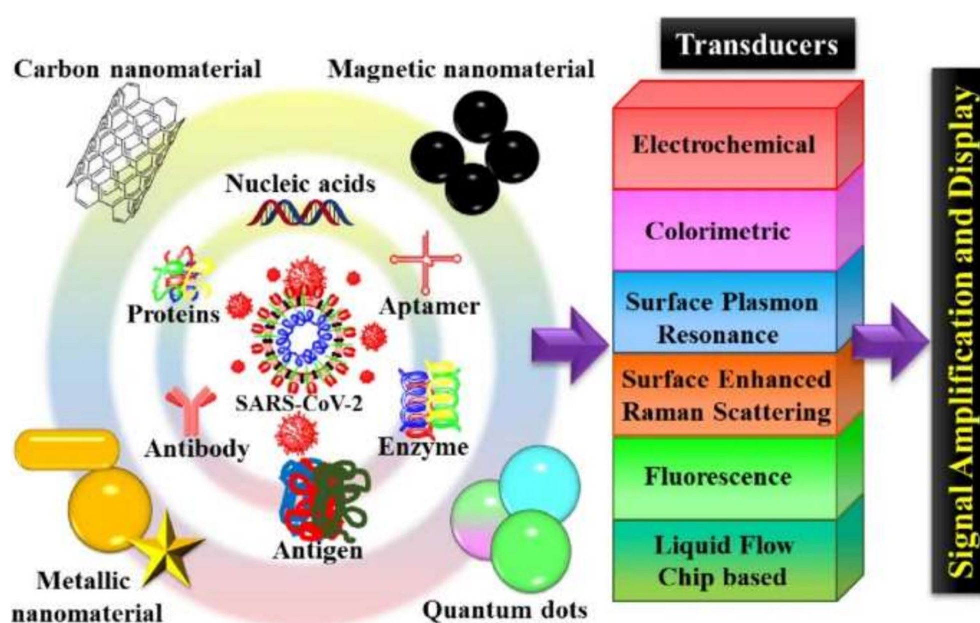

Fig. 1 This figure illustrates a range of rapid, accurate, specific, and sensitive optical nanobiosensor-based diagnostic tools for pathogen detection [39]

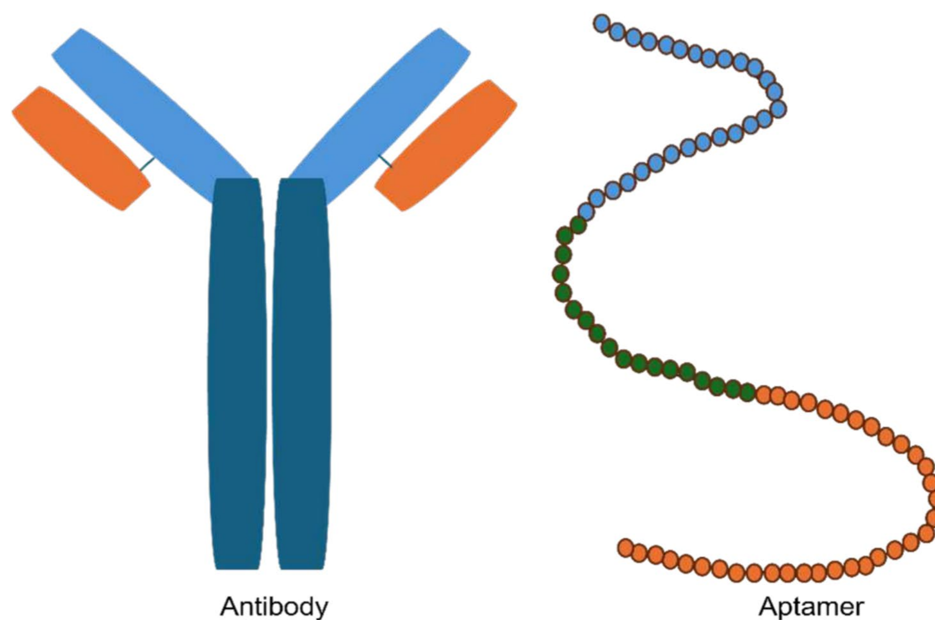

Fig. 2 Structural diagram of an antibody and an aptamer

These chains form variable regions (also known as paratopes) which are directed for attachment onto antigens, which have a specific structure called an epitope [43, 45, 46]. The structure of the antibody allows it to bind to the epitopes (on the antigens) to either neutralize the pathogenic microorganisms or to mark them for other immune responses [45–47]. This binding is highly specific, enabling antibodies to target specific pathogens, cells, or molecules. Antibodies produced for immune response (by B cells) against pathogens are often polyclonal, with the function of recognizing and binding to different epitopes of the same antigen [43, 45, 46, 48]. Similarly, identical B cells can produce monoclonal antibodies that target single or individual epitopes on an antigen. Their production and development as well as their high specificity and affinity make antibodies ideal for use in diagnostic assays, therapeutic applications, and research, including ELISA (Enzyme-Linked Immunosorbent Assay) and immunohistochemistry [42–48]. They are also fundamental in therapeutic applications, such as in the development of monoclonal antibody drugs, and are key tools in biomedical research. In contrast, aptamers (also known as chemical antibodies) are nucleic acids that are single-stranded with the ability to bind to their target through specific 3-dimensional (3D) conformations [24, 49, 50]. In addition, aptamers are usually 20 to 100 bases long and can make strong interactions with specific targets thus mirroring the natural interactions that occur between antigens and antibodies. Aptamers, unlike antibodies, interact with their target molecules through non-covalent connections, such as hydrogen bonds and van der Waals forces [42, 51]. Furthermore, for better binding affinities, they form 3D conformations (such as hairpins or loops) on their targets [42, 51]. Besides, the structural complementarity of aptamers, electrostatic interactions, and aromatic rings stabilize the complex formed between aptamers and the target molecule during binding [52, 53]. It is important to note that the binding of aptamers to their targets is highly specific and characterized by high affinities and dissociation constants/values (kd) [54, 55]. The dissociation constants/values indicate the strength of the interactions between the target and the aptamer. This is noted by an increase in binding affinity which results in a decrease in the dissociation constant [56]. This further enables aptamers to be able to distinguish subtle structural differences in/on the target [54, 55, 57]. In addition, one of the main characteristics of aptamers, that sets them apart from other synthetic receptors or biorecognition elements, is that they are characterized by a phenotype-to-genotype connection [58]. This simply means that they are sequence-specific (genotype) and their ability to fold into different conformations (phenotype) allows specific functions that further allow for better target recognition properties [56]. Some properties of aptamers have been said to be better than those of antibodies when they are compared and thought about for use in biosensing and/or diagnostic applications (Table 1) [50, 59, 60]. Some of these advantages include aptamers being chemically and structurally stable when compared to antibodies that easily become denatured. Similarly, conditions such as changing salt concentrations, temperature, and chelating agents lead to the permanent denaturation of antibodies while aptamers retain their native conformation [24, 50, 59–61]. In addition, aptamer production does not require animals for their production because they are synthesized in vitro. This further decreases the cost and the time spent on the production of aptamers relative to the production of antibodies.

Table 1 This table presents a concise comparison of the benefits and drawbacks of utilizing aptamers in biosensing applications as opposed to antibodies [24, 50, 59–61]

Characteristic	Aptamer	Antibody
Nature	Chemical (ssDNA/RNA, 20–100 nt/6–30 kDa)	Biological (Proteins, 490–600 nt/150–180 kDa)
Size	Up to 2 nm long	Up to 15 nm long
Structural conformations	Secondary structures (loops, hairpins, stems)	Y-shaped molecules (four polypeptide chains)
Targets	Proteins, ions, organs, cells, small molecules	Immune system molecules (antigens)
Binding affinity	High	High
Specificity	High	High
Synthesis process	Chemical *in vitro* (SELEX)	Biological *in vitro* (lab animals)
Duration of synthesis	Up to 8 weeks	Up to 6 months or longer
Other properties	Long shelf life, Heat-stable, temperature-resistant, Modifiable without decreasing binding affinity	Short shelf life, Not heat stable, temperature-resistant, Limited modifications before losing binding affinity

2.2 Selection and synthesis methods for aptamers

The selection of aptamers is usually through interactive methods that mimic natural evolution, referred to as Systematic Evolution of Ligands by Exponential Enrichment, also referred to as SELEX [42, 49, 56]. The selection process takes place over several weeks to months until a high-affinity aptamer is produced [42, 49, 56, 62, 63]. Furthermore, post-SELEX modifications, which include chemical reactions to increase the stability of the aptamer and its application often take place before the aptamer can be used for various applications [49, 62, 64]. The principle of the SELEX method starts with randomized ssDNA or RNA nucleotides (from a nucleotide library) with molecular weights between 6 to 30 kDa. These randomized nucleotides are sequence-specific at the 5′ and 3′ ends therefore making them important for determining the primers required for amplification using polymerase chain reactions (PCR) [42, 49, 65]. The selection process for RNA and DNA-based aptamers differ in terms of the chemical nature of the library used and the amplification process. For example, RNA-based aptamers are amplified using reverse transcription (RT-PCR) instead of conventional polymerase chain reaction (PCR) used for DNA-based aptamers. In addition, both DNA and RNA-based aptamers offer key advantages such as DNA aptamers being chemically stable and cost-effective in comparison to RNA aptamers which are more specific and have higher binding affinities for their target molecule [42, 50, 59, 66–68]. The most common SELEX method is conventional/classic SELEX which is a protein-based SELEX process. There are four classes of SELEX-based methods depending on the isolation, purification, and use of the aptamer with the target molecule [42, 65, 69]. These four classes include capillary electrophoresis SELEX, capture SELEX, magnetic-bead SELEX, and cell-SELEX [42, 65, 69]. Capillary SELEX is used when the interaction of the aptamer and RNA/DNA target does not require immobilization. In contrast, Capture-SELEX is used when the interaction between the aptamer and the target (DNA/RNA) requires immobilization. Magnetic-bead-SELEX, on the other hand is used when only the target requires immobilization. Finally, when the target molecule is not purified, the SELEX process used is referred to as cell-SELEX [69]. The SELEX process consists of several processes/steps required to generate an aptamer that is target-specific with a high binding affinity for the target molecule (Fig. 3) [49, 56].

2.3 Hybrid systems

Biosensing systems that capture both antibodies and aptamers on the same sensing platform are called hybrid systems [49, 70, 71]. Hybrid biosensing systems are also referred to as sandwich assays and/or dual-mode biosensing systems [70]. In recent years, hybrid systems have been made using a sandwich configuration, which relies on the target analyte being bound to the first capture probe followed by an amplified signal produced by a secondary reporter and capture probe [42]. Many of these hybrid systems consisted of antibody-antibody sandwich assays, however, the substitution of an aptamer as one of the capture probes has been reported as advantageous for many biosensing platforms [70, 71]. Furthermore, these aptamer-antibody sandwich assays usually require dual sites of recognition on the target [50, 72]. On several biosensing platforms, aptamer-antibody sandwich assays have been used for the detection of proteins, antibodies, and other microorganisms [70–77]. Many of these hybrid systems use aptamers as their primary capture probe,

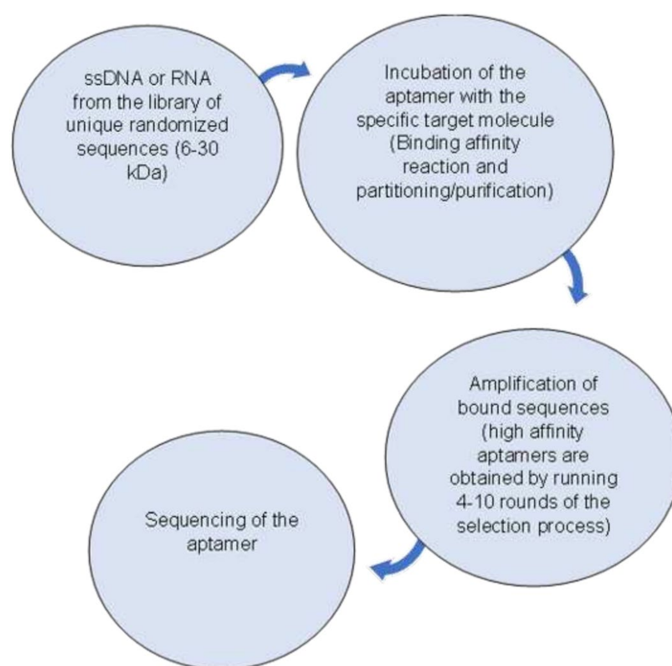

Fig. 3 Classic/Conventional SELEX process of producing aptamers. The production of aptamers simplified into 4 steps. These steps include: (1) randomized and unique sequence selection, (2) incubation, binding affinity, and purification/partitioning, (3) amplification and (4) sequencing of the aptamer

while the antibody acts as the secondary reporter and capture probe. This is because antibodies have higher molecular weights and are generally larger compared to aptamers, which aids in them (antibodies) producing an amplified signal during biosensing [65]. Several studies have compared hybrid biosensing platforms with aptasensors characterized for specific targets [78]. Common biosensing platform configurations consist of an immobilized capture antibody on the transducing element or electrode (depending on the type of biosensor) and an aptamer bound to the capture analyte. In addition, these hybrid biosensing configurations induce a cascade of reactions that allow for highly sensitive detection [58]. Although hybrid systems/sandwich assays are more complex and require multiple steps for detection to occur, their use has better analytical performance than other types of biosensing platforms. A study investigating the analytical performance between different configurations of an SPR-biosensor for protein detection (C-reactive protein) reported that on a gold nanoparticle enhanced platform, the limits of detection obtained were 1 nM and 10 pM for a standard format biosensor and a hybrid system biosensor, respectively [52, 53]. Similar dual-mode biosensing platforms have been used in several studies targeting clotting factors[[56], human epidermal growth factor receptors [58], and Alzheimer's disease biomarkers [79] amongst other biorecognition elements. Challenges of using aptamers with small molecular targets include lower structural complexities for molecules less than 1KDa, fewer to limited moieties viable for conjugation due to the reduced surface area and weaker binding interactions. In addition, the limited number of functional groups within small molecules limit the conjugation ability of the aptamer and target. Similarly, although antibodies can detect the small molecular targets, difficulties in creating antibody pairs can lead to lower assay specificity and sensitivity, and the requirements of complex processing of the sample for small molecular target detection.

3 Opto-aptamer biosensors

Optical biosensors have been used quite extensively in a wide range of applications [80–84]. They play a pivotal role in biochemical and molecular diagnostics, agricultural studies, defense and security, veterinary studies, evaluating food and monitoring the environment. In biosensing work, a range of methods have been devised to attach chemical markers to molecules, enabling the precise measurement of interactions between biomolecules. These include fluorescent labeling [85], radioactive labelling [86], enzymatic labeling [87], biotin-streptavidin, gold nanoparticle labeling, quantum dot labelling, chemiluminescent labelling, and mass tags. However, these markers can sometimes interfere, altering the way molecules connect with their intended targets. Moreover, marking molecules for extensive research can be intricate, time-consuming, and constrained by various aspects. Label-free bioanalysis methods do without the need for

such markers, making it possible to use natural biomolecules in a wide range of biomedical applications. This is a key motivation for moving to optical biosensors, which have the property of being label free.

Several label-free techniques have been created, such as surface plasmon resonance (SPR) [88], localized surface plasmon resonance (LSPR) [89], Raman spectroscopy [90], the quartz crystal microbalance [91], biolayer interferometry [92], surface acoustic waves [93], fluorescence-based biosensors (e.g., FRET, FLIM) [94], silicon nanowires [95], and photonic crystals (PC) [96]. They are used for studying different types of binding interactions, including protein-protein, protein-aptamer, protein-small molecule, carbohydrate-protein, protein-nucleic acid, protein-lipid, and carbohydrate-protein, among others. Incorporating these nucleic acid aptamers into various sensing technologies enhances their utility [97]. These aptamers allow devices to be reused without losing effectiveness, making these devices potentially recyclable. Aptamer-based methods have been developed for a range of detection applications, including fluorescence, SPR, surface-enhanced Raman spectroscopy (SERS), colorimetry, and electrochemistry. In this review section the authors look at the application of optical biosensors including SPR, LSPR, PC and Raman spectroscopy in aptamer-based diagnostics.

3.1 Aptamer-based surface plasmon resonance

A surface plasmon resonance-based biosensor is an optics-based diagnostic technology [100]. In a surface plasmon resonance setup, light is directed towards a high-density medium, which is typically a prism. Upon incidence with the prism, the light is refracted towards the prism base, which is coated with a thin metal layer (Fig. 4). It is on this metal layer where the binding interactions of the biosensor occur. When the light hits this metal surface from a specific angle of incidence, the light couples to the oscillating electrons in the metal film. This coupling results in an evanescent wave that propagates on the surface of the biosensor, which is commonly referred to as the surface plasmon wave. This phenomenon can be observed as a drop in the intensity of the reflected light beam (Fig. 5). The resonance dip is observed. This resonance dip profile gives information about the binding interaction on the biosensor surface, i.e., as binding interactions occur, the position of the dip shifts (Fig. 5). This shift in the dip position can serve as a confirmatory test for the binding interaction. The shift can also be plotted as a sensorgram, which monitors the shift in the resonance dip position as a function of time. This allows for the generation of binding kinetics, which are useful for understanding binding activity more fundamentally. There have been many attempts to optimize the performance of SPR, ranging from improvements to the technical setup, integration of nanoparticles, and the use of quantum states of light. This study presents a dual-transducer aptasensor that integrates plasmon-enhanced fluorescence (PEF) and electrochemical (EC) transduction mechanisms for detecting the SARS-CoV-2 spike protein [101]. The biosensor utilizes a novel nanoimprint lithography technique to fabricate gold nanopit arrays (AuNpA) with unique fringe structures. These structures allow the surface plasmon polariton peak to overlap with the excitation peak of the C7 aptamer's fluorophore, methylene blue (MB). The sensor demonstrated enhanced fluorescence, with intensity five to seven times greater over the AuNpA and fringe structure compared to a flat gold surface. In addition to fluorescence detection, MB also served as a redox probe for the EC transducer, marking the first use of such a dual-transduction label. The PEF transducer achieved a detection limit of 0.07 fg/mL within a range of 1 fg/mL to 10 ng/mL, while the EC transducer extended the dynamic range to 100 ng/mL with a detection limit of 0.15 fg/mL. This innovative dual-transducer platform highlights a scalable fabrication method for nanostructures and offers a versatile solution for advanced biosensing applications.

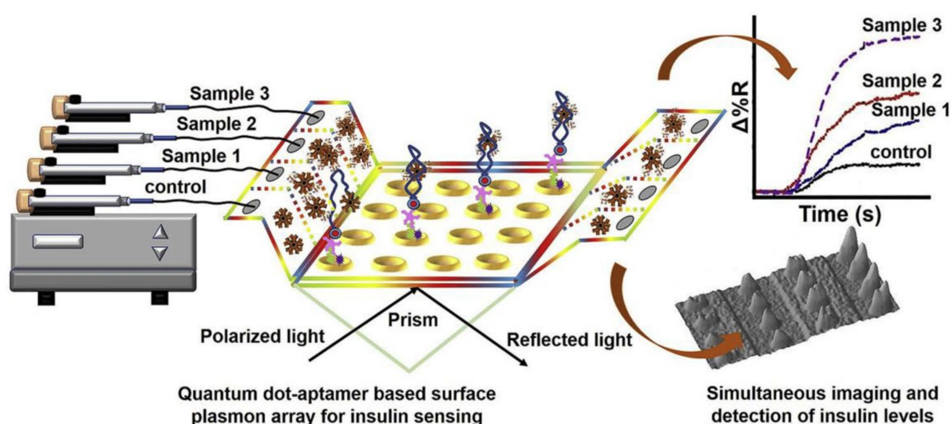

Fig. 4 The image shows an SPR setup in which insulin was found in serum samples from individuals with diabetes using an array chip that included QDs [98]

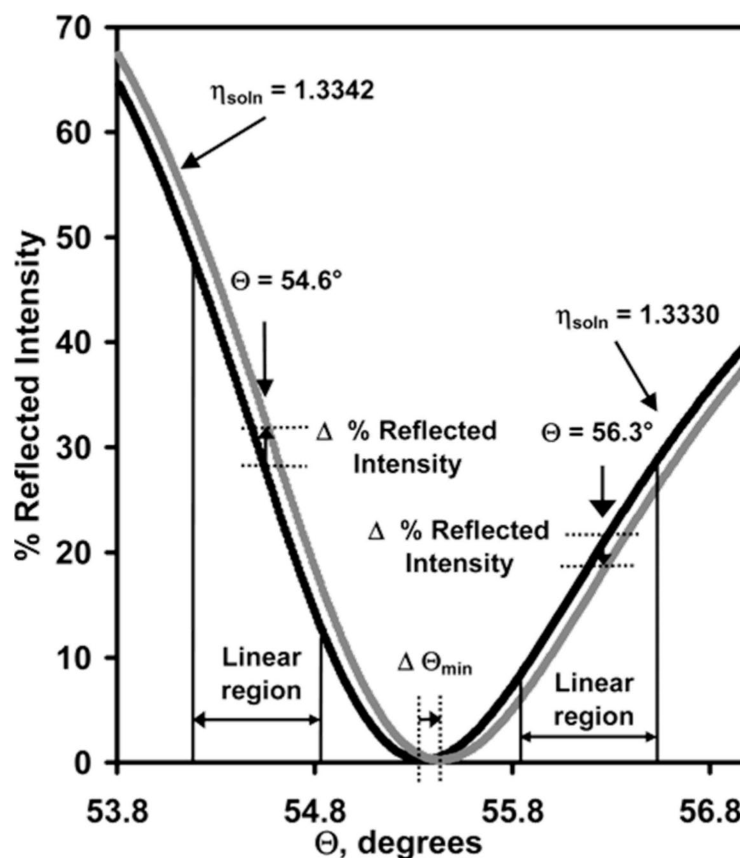

Fig. 5 The image depicts an instance of the operational mechanism of reflectivity-based surface plasmon resonance imaging (SPRi). SPR reflectance curves for two materials in contact with the gold surface that have varying refractive indices are displayed here vs. incident angle. [99]

The growing success of using antibody-based SPR detection has led to increased interest in aptamers in research circles. Aptamers, which are novel combinations of nucleic acid and peptide molecules, are gaining traction in diverse sensing applications, from molecular diagnostics to analytical chemistry. They are considered potential alternatives to antibodies. Specifically, nucleic acid aptamers form unique and stable 3D structures. These structures allow them to interact effectively with a variety of molecular targets, including small ions, organic compounds, and larger proteins or complex molecules. Producing them, usually using combinatorial nucleic acid libraries and *in vitro* selection methods, is generally more cost-effective than manufacturing and purifying antibodies.

Nucleic acid aptamers offer additional benefits, particularly in terms of their chemical modifiability. Their target-binding capabilities can be maintained as they are tagged with fluorescent molecules or gold particles and incorporated into nucleic acid nanostructures. Furthermore, unlike protein-based antibodies and nanobodies, nucleic acid aptamers can recover from denaturation under harsh conditions. DNA aptamers, despite RNA aptamers being discovered first, are more commonly used in sensors due to their resistance to base-catalyzed hydrolysis.

The simplicity of aptamer-based SPR methods has led to their widespread use. This review discusses SPR sensors utilizing aptamers for detecting biological and chemical substances. Many experts in SPR have published reviews emphasizing the benefits of its working principles, setups, and various applications. Additionally, there's significant literature on enhancing SPR sensitivity, especially through integration with other techniques, like the use of nanomaterials. However, there are relatively few reviews focusing specifically on aptamer-based SPR sensors. Given the extensive range and diversity of reported aptasensors, the review concentrates on two main detection methods: direct (one-site binding) and sandwich (two-site binding) (see Fig. 6). Lastly, it addresses future challenges and potential developments in SPR aptasensors.

3.1.1 Direct (one-site binding) detection mode

The fundamental operation of SPR aptasensors is analogous to that of other sensor categories: aptamers are immobilized onto the sensor substrate, where they selectively identify and attach to their particular target. Subsequently, an optical transducer converts this interaction into measurable signals. This direct detection method is faster than other SPR sensing

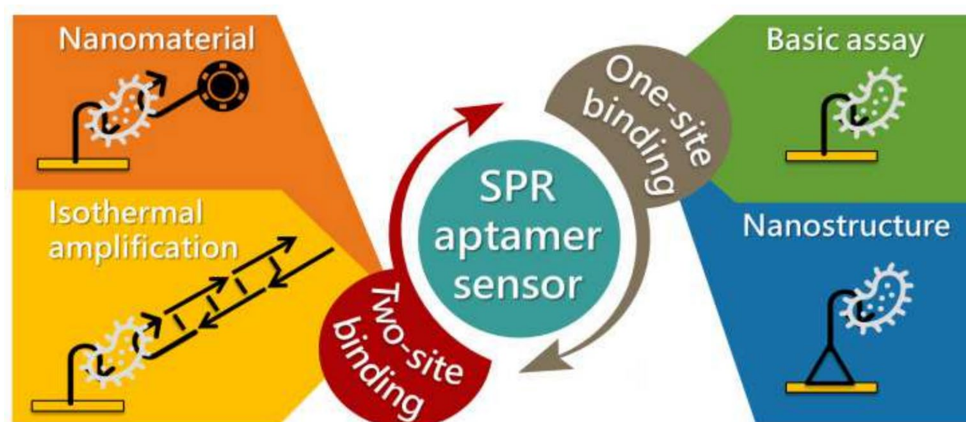

Fig. 6 Overview of various aptamer-based SPR sensor types. This was taken from [100]

techniques because it involves fewer processes and requires less time. Small molecules are especially pertinent in this context since they often attach to aptamers in a one-site arrangement due to the restricted space available for interaction with a second molecule. As a result, many SPR aptasensors using this direct method have been created. A biotin-modified aptamer probe on an avidin-coated chip was used by Wu et al. [102] and Ashley et al. [103] to find aflatoxins (which is found in vinegar) and lysozymes (found in milk). This was done by streptavidin-biotin interactions. In another example, RNA aptamers were tethered to the sensor surface using thiol-gold bonds to assess the binding kinetics of different molecules. However, due to SPR's sensitivity to changes in refractive index at the sensor surface, which depend on the mass of the bound component, detecting small molecules is a challenge.

Duanghathaipornsuk et al. [104] explored the impact of binding affinity strength on sensor performance. DNA nanocages were created for SPR sensing of hemoglobin and glycated hemoglobin to make the bonds between aptamers and their target proteins stronger and more stable. These nanocages had a 3D DNA structure with two custom cavities that held aptamers that were made to bind and capture target proteins more tightly, which improved binding and selectivity. This DNA aptamer-embedded origami cage structure showed a lot higher binding affinity and selectivity toward glycated hemoglobin, which could be a step forward in making SPR sensors work better. Multiplex molecular sensing systems are designed to simultaneously detect various targets from a single sample, reducing the sample volume needed and speeding up detection times. There's a growing interest in using SPR sensors for biomolecule detection. For instance, Chen et al [105]. developed a microfluidic SPR system with four chambers, using RNA aptamer microarrays for detecting human thrombin and vascular endothelial growth factor (VEGF) proteins. This microfluidic system makes it easy to make RNA aptamers quickly and directly using T7 RNA polymerase surface transcription. This makes it possible to sense multiple proteins in one step. While a single SPR aptamer array can analyze multiple targets concurrently, the reliability of these SPR chips largely depends on the reproducibility of the sensor array. To solve this problem, Inoue et al. [106] created an SPR aptamer array using an inkjet spotter that precisely controls where the aptamer solution goes and how much of it there is. They used a portable, multi-analysis SPR device with a capillary-driven flow chip to find thrombin and looked at SPR signals at different thrombin concentrations at the same time. This method makes SPR arrays more reliable by cutting down on the number of steps that need to be done by hand and using BlockAce reagent, which is commonly used in ELISA technology, to separate biomolecule spots. This raises the detection limit to the same level as other SPR sensors (1 nM).

Non-specific binding in SPR arrays is a common problem that can compromise assay accuracy. A study by Duanghathaipornsuk et al. discovered that adding DMOL to a self-assembled monolayer-modified array surface lowers the amount of non-specific protein binding and gives the aptamers more freedom to interact with their targets. Moreover, SPR arrays are not just limited to sensing; they can also be used to determine the optimal surface density of aptamer strands. Gyurcsányi et al. [107] showed that the best measured affinity depends on the size of the target and is reached by having the right number of aptamers on the surface. In general, the SPR signal should go up as the concentration of target molecules goes up. This is because the SPR signal is related to the molecular weight and the rise in the refractive index. Nonetheless, atypical SPR signals were reported in Bonnet et al.'s [108] study on tyrosinase detection. They discovered that a negative SPR signal which is picked up during analyte detection could be attributed to the conformational change of the aptamers. The aptamer changed shape, which caused the combined refractive index increase of the small molecule/aptamer complex to be different from the sum of the increases in the individual components. These

findings offer fresh perspectives and insights into how the non-linear nature of refractive index increments can influence SPR signal variations. Typically, SPR aptasensors operating in direct mode for biomolecules function at nanomolar levels. Therefore, there's significant effort directed towards enhancing the SPR detection response, for example through nanomaterial or enzyme amplification. The specifics of these methods are discussed in the following section. The table 2 shows a list of all the known aptamer surface plasmon resonance (SPR) tests that use the one-site binding arrangement to find biological compounds.

3.1.2 Sandwich (two-site binding) sensing mode

Using a sandwich format with two aptamers targeting different sites on the same molecule can enhance the sensitivity of SPR aptasensors. In this configuration, a single aptamer functions as a capture probe and is affixed to the gold surface. The second aptamer, which serves as a reporting probe, is frequently connected to signal-amplifying markers such as nanoparticles. Even though these probes usually have unique oligonucleotide sequences, certain dimeric proteins, such as platelet-derived growth factor-BB (PDGF-BB), possess two identical binding sites. Therefore, a PDGF-BB sandwich assay can be demonstrated with just one type of aptamer. Nonetheless, if the target molecule has only a single aptamer binding site, an aptamer-antibody sandwich assay can be employed, combining an aptamer with an antibody. Table 3 displays a compilation of documented aptamer surface plasmon resonance (SPR) tests utilizing the two-site binding arrangement for the identification of bio/molecules.

3.2 Localized surface plasmon resonance (LSPR)

Localized surface plasmon resonance employing noble metal nanostructures for label-free biomolecular assays has garnered notable interest in scientific research [128–130]. LSPR biosensors function through either colloidal aggregation or alterations in the local refractive index. Organic molecules, having higher refractive indices than buffer solutions, modify the local refractive index upon binding to plasmonic nanoparticles [131]. This alteration manifests as a red-shift in the extinction and scattering spectra, providing a basis for LSPR shift-based sensing [132]. These sensors offer multiple advantages such as multiplexed detection and compatibility with microfluidics, among others. While LSPR shift-based assays have numerous benefits, their sensitivity is significantly lower compared to other plasmonic biosensors. Efforts to enhance sensitivity have been varied [133]. One approach is optimizing the refractive index sensitivity of nanoparticles through size and shape adjustments. Another involves employing single nanoparticle sensors, which promise better detection limits and potential for multiplexed assays. Moreover, increasing the refractive index change through molecular binding has shown promise in boosting LSPR sensitivity. Techniques include augmenting the molecular mass attached to nanoparticles, utilizing chromophore coupling, and creating nanoparticle pairs to exploit distance-dependent plasmonic coupling. Methods to augment LSPR sensitivity have been previously suggested which include constructing aptamer-antigen-antibody sandwich structures [134–136]. By attaching an antibody to an antigen, this significantly increases the target molecule's mass, thus enhancing LSPR shifts. This technique has improved the detection limit of

Table 2 List of aptamer SPR assays with the one-site binding configuration for the detection of bio/molecules (NR: not reported) [100]

Immobilized aptamer probe	Analyte	Response time	Detection range	Limit of detection	Ref.
DNA	Kanamycin and Neomycin	10 min	0.002–0.48 μg/mL (Kanamycin), 0.003–0.72 μg/mL (Neomycin)	0.89 ng/mL (Kanamycin), 1.55 ng/mL (Neomycin)	[109]
DNA	*Pseudomonas aeruginosa*	70 min	10-10^3 cfu/mL	10 cfu/mL	[110]
DNA	Thrombin	60 min	5–20 nM	0.7 nM	[111]
DNA	Glycated Hemoglobin (HbA1c)	50 min	73–294 nM	2.55 nM	[112]
DNA	*Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*)	80 min	10^5–10^8 cfu/mL, 10^6–10^8 cfu/mL	10^5 cfu/mL (*E. coli*), 10^6 cfu/mL (*S. aureus*)	[113]
DNA	Lysozyme	20 min	0.05–1 μg/mL	0.035 μg/mL	[114]
DNA	L-tyrosinamide	10 min	0.010–250 μM	10 nM	[108]

Table 3 List of aptamer SPR assays with the two-site binding configuration for the detection of bio/molecules (NR: not reported) [100]

Sandwich design	Aptamer type	Response time	Detection range	Limit of detection	Ref.
Antibody-magnetic nanoparticle/insulin/aptamer	DNA	13 min	0.8–250 pM	0.8 pM	[115]
Aptamer I-gold nanorod/norovirus capsid protein/aptamer II	DNA	50 min	70–500 aM	50 aM	[116]
Aptamer I-dual gold nanoparticle (T30-AuNP/A30-AuNP)/exosome/aptamer II	DNA	60 min	NR	5×10^3 particles/mL	[117]
Aptamer I-polydopamine-functionalized gold nanoparticle/exosome/aptamer II	DNA	40 min	NR	5.6×10^5 particles/mL	[118]
Antibody-gold nanocage (AuNC), gold nanorod (AuNR), or gold quasi-spherical nanoparticles (AuQNP)/thrombin/aptamer	DNA	25 min	1 aM-1 fM (AuQNP) 10 aM-10 fM (AuNR) 1 fM-1 pM (AuNC)	1 aM (AuQNP) 10 aM (AuNR) 1 fM (AuNC)	[119]
Aptamer I-dual gold nanomaterials (T20-AuNR/A30-AuQNP)/thrombin/aptamer II	DNA	100 min	0.1–2 aM	0.1 aM	[120]
Antibody-gold nanocube/B-type natriuretic peptide/aptamer	DNA	35 min	1 aM-500 nM	1 aM	[121]
Folic acid-magnetic nanoparticle breast cancer cells (MCF-7)/aptamer	DNA	333 min	5×10^2-10^4 cells/mL	5×10^2 cells/mL	[122]
Aptamer I-gold capped magnetic nanoparticle/thrombin/aptamer II	DNA	60 min	0.1–100 nM	0.1 nM	[123]
Aptamer I-near-infrared quantum dot/C-reactive protein/aptamer II	DNA	183 min	5–5000 fg/mL	5 fg/mL	[124]
Aptamer-graphene oxide/prion disease-associated isoform/intramolecular thiol group	DNA	40 min	4.24×10^{-5}-4.24×10^{-2} nM	4.24×10^{-5} nM	[125]

thrombin substantially. Additionally, using an aptamer as a capture molecule allows for the biosensor's reuse, enhancing both reproducibility and sensitivity. Table 4 shows a comparison of biosensing using LSPR with antibodies and aptamers.

Noble metal nanoparticles (NPs) have become crucial elements in transducer technology for efficient sensing, because of their unique optical features. LSPR-based sensors, particularly, have been employed for the quantitative detection of biological or chemical substances, offering advantages such as heightened sensitivity and the ability to perform real-time and label-free detection. LSPR sensors, unlike conventional SPR biosensors that utilize thin gold films, are not sensitive to temperature variations and can be miniaturized, leading to increased detection efficiency and reduced operational costs.

The demand for analyzing multiple targets simultaneously, especially in diagnostic and analytical fields, has driven the need for multiplex detection platforms as well ashigh throughput devices [137]. These devices aught to have the capacity to analyze large numbers of samples or multiple analytes concurrently. However, current LSPR-based sensing techniques, such as those using gold nanorod-based multiplex detection, are somewhat limited in the number of targets they can detect [138, 139]. Some methods have involved immobilizing NPs on sensor chips with physical divisions to facilitate parallel detection. Although these methods have somewhat achieved high throughput, they often involve complex processes due to non-specific target binding and laborious washing steps. A significant challenge in the field remains the development of sensitive and high-throughput LSPR-based detection methods that are compatible with standard laboratory equipment, particularly in detecting small molecules. Using NP-antibody conjugate sandwich assays has made LSPR sensors more sensitive, but it has also added more steps to the process [140]. In contrast, nucleic acid–based assays, like aptamer-based competitive replacement assays, have shown significant potential in enhancing sensitivity for electrochemical biosensors and SPR systems [141]. Aptamers, being oligonucleotides that specifically bind to targets, offer advantages over antibodies, including their ease of synthesis and ability to interact with non-protein targets.

Researchers previously created a novel biosensor chip array for detecting biomolecules using microplate readers. The biosensor chip array is based on aptamers and operates without walls, allowing for efficient, high throughput, and sensitive detection [136]. The LSPR array chip, which lacks walls, was fabricated by attaching plasmonic nanoparticles to a glass slide with a hydrophilic-hydrophobic pattern. The chip utilizes a double-gold nanoparticle system in an aptamer-based competitive replacement test to enhance the sensitivity of LSPR [136]. The researchers utilized adenosine triphosphate (ATP) and its matching aptamer as a model system to showcase efficient and compact detection on a large scale. This study presents the development of a sensor using a wall-less array structure and a double-gold nanoparticle-enhanced system. The sensor is designed to detect small molecules with high sensitivity, using aptamers, and can be operated with ordinary laboratory equipment in a simple and efficient manner [136]. Table 5 shows areas of application for antibody and aptamer based LSPR biosensors.

3.3 Fluorescence-based techniques (e.g., FRET, FLIM)

Fluorescence polarization-based bioassays present an innovative and promising approach for bioanalytical applications [151–155]. These assays operate by detecting changes in the rotational dynamics of fluorophores following their interaction with an aptamer and its target molecule (Fig. 7). When an aptamer binds to a particular target, it can alter the polarization of fluorescence, providing a measurable indicator of the target's concentration. This method relies on illuminating the reaction with plane-polarized light and assessing the resulting fluorescence [151–155]. Polarized light is absorbed more efficiently by molecules aligned with the polarization plane. If these molecules maintain their orientation upon excitation, their fluorescence will also exhibit polarization, as described by Henderickson et al [151]. This technique has been extensively reviewed, highlighting advances and the application of new methodologies for detecting various biochemical entities like metal ions, enzymatic activities, and nucleic acids.

Moreover, these bioassays are highly valued for their ability to generate specific aptamers in large quantities, giving researchers flexibility in choosing aptamers by modifying interaction conditions [152]. For example, Liu et al [156]. developed a quick, fluorescence polarization-based assay to detect bisphenol A, a significant health hazard, using a specially labeled DNA aptamer. This binding alters the fluorescence polarization due to changes in the interaction within the molecule, proving effective for rapid detection with high specificity. Similarly, Pengfei Ma et al. created an aptasensor for identifying *Weissella viridescens* bacteria in food products, utilizing a biotin-labeled aptamer and fluorescence-labeled cDNA to achieve a quantifiable response correlating with bacterial presence [157]. Such innovations demonstrate the broad utility and adaptability of fluorescence polarization assays in modern bioanalytical science.

Fluorescence-based techniques such as Förster Resonance Energy Transfer (FRET) [158] and Fluorescence Lifetime Imaging Microscopy (FLIM) are significant tools in the field of biological research, particularly when combined with aptamers and antibodies [153]. FRET is employed to study molecular interactions like protein-DNA and protein-protein

Table 4 Comparison of biosensing using LSPR with antibodies and aptamers [126, 127]

Parameter	Antibody-based biosensing	Aptamer-based biosensing
Detection method	Surface plasmon resonance changes in metallic nanostructures	Binding of target molecules to aptamers causing measurable changes
Sensitivity	High, due to localized surface plasmon resonance effects	High, due to strong binding affinity of aptamers to specific targets
Specificity	Dependent on the surface chemistry of nanostructures	Very high, due to the unique three-dimensional structures of aptamers
Advantages	Real-time detection, no need for labels, temperature insensitivity, potential for miniaturization	High specificity, reusability, stability, ease of synthesis, potential for non-protein target detection
Disadvantages	Potential issues with stability and reproducibility, limited by the properties of the nanostructures used	Sensitivity can be affected by environmental conditions, limited by the aptamer's affinity to the target
Applications	Detection of biological and chemical molecules, environmental monitoring, medical diagnostics	Drug discovery, medical diagnostics, environmental monitoring, food safety

Table 5 Example studies involving aptamer-Based LSPR biosensing

Reference	Target analyte	Key findings
[142–144]	ATP (Adenosine Triphosphate)	Demonstrated a novel LSPR-based sensor using gold nanoparticles and ATP-specific aptamers, achieving high sensitivity and specificity in detection.
[145–148]	Cancer Biomarkers	Developed an aptamer-functionalized LSPR platform for the detection of specific cancer biomarkers, highlighting the potential for early cancer diagnosis.
[141, 149, 150]	Heavy Metals	Utilized aptamer-conjugated LSPR sensors for the detection of heavy metals in water, showing promise for environmental monitoring applications.

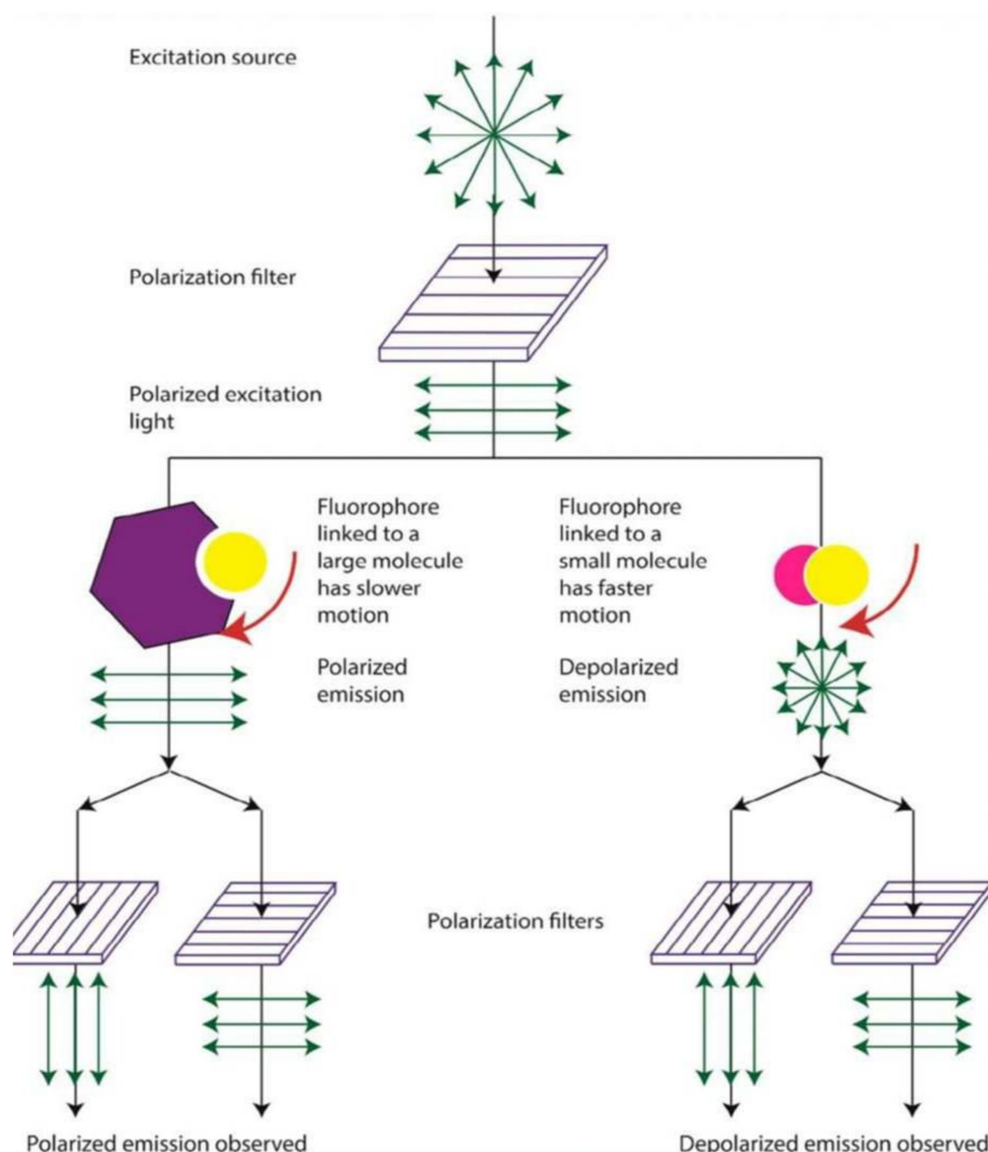

Fig. 7 Diagram outlining the idea behind measuring fluorescence when exposed to plane-polarized light [151]

interactions and can measure distances between molecules on a nanoscale. It is a process where energy is transferred from an excited donor fluorophore to a nearby acceptor fluorophore without radiation. FRET efficiency is heavily dependent on the proximity of the donor to the acceptor, typically less than 10 nanometers, and their relative orientation to each other. FLIM, on the other hand, provides a more quantitative approach by measuring the decay time of the donor fluorescence in the presence of an acceptor. FLIM is less affected by fluctuations in fluorophore concentration, making it advantageous for accurately quantifying FRET events. FLIM-FRET, which combines both methods, offers enhanced data quality and precision. This combination allows for the sensitive detection of biomolecular interactions *in vitro* and *in vivo*, creating opportunities to explore the dynamics of cellular and molecular processes with high specificity.

Aptamers are particularly interesting in this context as they are nucleotide sequences that can be engineered to bind with high specificity and affinity to their target molecules, which can be proteins, small molecules, or even cells. When used in FRET-based assays, they can act as the recognition element, and their binding to the target can be detected by FRET if they are tagged with appropriate fluorophores [153]. The combination of aptamers with FRET and FLIM allows for the creation of highly specific and sensitive biosensors that can be used in a variety of applications, including disease diagnostics and the monitoring of therapeutic interventions. The use of aptamers and antibodies in FRET and FLIM-based techniques has significantly advanced the capabilities in diagnostics and molecular imaging. Aptamers offer certain advantages over antibodies in these applications due to their chemical synthesis, ease of modification, and stability, making them well-suited for creating complex biosensors for various analytes.

3.4 Raman spectroscopy (e.g., SERS)

Raman spectroscopy combined with aptamers and antibodies enhances molecular detection through Surface-Enhanced Raman Scattering (SERS). Aptamers are particularly beneficial due to their easy synthesis, modifications, and high stability, affinity, and specificity. SERS sensors leveraging aptamers have been applied in detecting small molecules, pathogens, mycotoxins, and tumor markers, and also in photothermal therapy of tumors. They overcome challenges of label-free SERS sensors in complex systems or low-concentration scenarios by improving target selectivity and analysis sensitivity [159, 160]. Surface-Enhanced Raman Scattering (SERS) is often employed alongside aptamers for the detection of small molecule analytes. The basis of the Raman signal is photon scattering, influenced by the electric cloud of a molecule, producing a distinct signal for each analyte. Historically, the weakness of the Raman scattering signal limited its sensitivity until the introduction of colloidal nanoparticles, which significantly boosted signal strength and sensitivity. Initially, nanoparticle-enhanced Raman scattering suffered from issues of specificity and reproducibility. However, these challenges have been addressed by integrating highly specific aptamers. Recent research demonstrated that nanoparticles linked with aptamers retain the same target affinity as free aptamers. In a specific application, SERS combined with a BPA-specific aptamer successfully detected bisphenol A-a common plastic byproduct-in human blood at concentrations as low as 600 femtomolar. This method shows potential for detecting various targets within complex biological samples.

3.5 Metal-enhanced fluorescence (MEF)

Metal-enhanced fluorescence (MEF) is a technique that leverages the interaction between fluorescent molecules and metallic nanostructures to enhance the emission intensity of fluorophores [161]. This method offers several advantages, such as increased sensitivity, extended photostability, and reduced photobleaching. MEF is achieved by placing fluorophores in proximity to metal surfaces, typically noble metals like silver or gold, which amplify the local electromagnetic field, resulting in an enhanced fluorescence signal. The coupling between the fluorophores and the plasmonic field generated by metallic nanostructures leads to significant improvements in detection limits for biosensing applications. MEF has found applications in bioimaging, molecular diagnostics, and biosensor platforms where high sensitivity and signal amplification are crucial [161]. This technique also shows promise for real-time monitoring of biological processes due to its ability to enhance weak fluorescence signals from low-abundance biomolecules.

3.6 Surface-enhanced infrared absorption (SEIRA)

Surface-enhanced infrared absorption (SEIRA) is a powerful technique used to amplify infrared absorption signals of molecules adsorbed on metallic nanostructures [161]. The SEIRA effect arises from the enhancement of local electromagnetic fields near the surface of metal nanoparticles, typically gold or silver, which boosts the vibrational modes of nearby molecules. SEIRA complements SERS by providing additional molecular fingerprinting capabilities in the infrared region. It is particularly useful for studying biomolecular interactions, detecting low-concentration analytes, and investigating surface phenomena. The integration of SEIRA into biosensing platforms offers high chemical specificity and sensitivity, making it suitable for applications in environmental monitoring, healthcare diagnostics, and chemical analysis [161].

3.7 Photonic crystals

A photonic crystal aptasensor combines photonic crystal structures with aptamers to create a sensitive device for detecting specific proteins. Photonic crystals manipulate light waves, while aptamers, which are nucleic acids, specifically bind to target proteins. This results in a highly precise and efficient biosensor that can detect proteins by monitoring changes in the crystal's optical properties due to aptamer binding. Aptamer-based photonic crystals have shown potential in diagnostics and environmental monitoring. A recent review discussed integrating aptamers with two- and three-dimensional photonic crystals, offering enhanced detection capabilities and precision [162]. Photonic crystals can also be integrated with other biosensors for better sensitivity [163].

3.8 Fibre-optics based aptasensors

Aptamer-based fiber-optic biosensors represent a significant advancement in biosensing technology. Fiber-optic platforms, especially plastic optical fibers (POFs), are perfect for using aptamers in biosensing because they are flexible, have a large numerical aperture, and can detect things well in proof of concept (POC) tests. This coupling allows the aptamer-POF sensors to monitor various targets, from environmental pollutants to disease biomarkers. For instance, SPR or LSPR sensors leverage fiber-optic properties to detect targets by measuring resonance wavelength shifts, providing high sensitivity and rapid response. Their compatibility with aptamers enhances their ability to identify targets accurately, even in complex samples. Such systems are being developed to detect viruses like SARS-CoV-2, cancer biomarkers, and vascular endothelial growth factors (VEGF), with applications spanning healthcare, environmental monitoring, and food safety. Researchers are also focusing on improving the robustness and cost-effectiveness of fiber-optic biosensors. Smartphone-based optical interrogation methods can provide portable and affordable solutions. Different fiber configurations, like U-bent, D-shaped, and tapered fibers, enhance the adaptability of the sensors to various environments and targets [164–166]. Aptamer-based fiber-optic biosensors are advancing toward more versatile, sensitive, and cost-effective solutions in biosensing, offering promising future applications in several fields.

3.9 Photonics integrated circuits

Aptamer-based photonic integrated circuits (PICs) offer remarkable potential for biosensing due to the unique features of aptamers and the integration capabilities of photonics. The small size of aptamers, their high stability, and their strong affinity for targets make them ideal for use in PICs. One example involves using S-shaped double-spiral resonators (DSRs) in PICs for biosensing. These structures are respond strongly to changes in refractive index, which makes them well-suited to detect target molecules through evanescent field sensing. When coupled with aptamers as molecular recognition elements, DSRs in PICs can achieve high specificity and sensitivity, allowing them to detect small volumes of target analytes like gases and liquids efficiently [167]. Moreover, integrating aptamers with DNA nanostructures has enabled the development of highly programmable and versatile platforms for biosensing. Such integration allows aptamers to recognize specific targets, and the resulting structures can be adapted for various sensing applications, including bioimaging and targeted cancer therapy [168]. These nanostructures, combined with the precision of PICs, form an advanced biosensing tool with the potential for significant advancements in healthcare diagnostics, environmental monitoring, and other fields.

3.10 Interferometers

Aptamer-based interferometers leverage the specificity of aptamers and the sensitivity of interferometric techniques for real-time, label-free biosensing. An example includes a nanoporous anodic alumina interferometric biosensor that uses aptamers immobilized on modified surfaces to detect thrombin in real-time. This approach offers high sensitivity due to the reflective interferometric spectroscopy (RIfS) technique, which detects changes in the refractive index. Such devices are promising for rapid and accurate detection of biomolecules, paving the way for advancements in diagnostics and environmental monitoring [169].

4 Application areas of aptamers in optical biosensing

Aptamers, single-stranded DNA or RNA molecules that bind to specific targets with high affinity, have become an essential component in optical biosensors. Their ability to bind a wide range of targets, including small molecules, proteins, and cells, makes them versatile tools for biosensing applications. This section provides an in-depth discussion of the key areas where aptamer-based optical biosensors have shown promising results, along with reported highlights from recent research studies. Table 6 shows the different application areas for aptamer and antibody detection.

4.1 Detection of small molecules

Detecting small molecules like toxins and drugs requires high sensitivity. Aptamer-based optical biosensors are effective due to their specificity and adaptability. One notable challenge is that many small molecules lack intrinsic fluorescence or chromogenic properties. Modern aptamer biosensors address this by employing advanced transduction schemes

Table 6 Comparison of antibodies and aptamers in different detection applications

Detection application	Antibodies	Aptamer	Differences in optical biosensor applications
Small molecules	Low binding affinity and specificity	Moderate binding affinity and high specificity	Aptamers are preferred over monoclonal antibodies because they can change their conformation (due to their tertiary structure) to fit small molecule-target binding.
Proteins and enzymes	High binding affinity and high specificity	High binding affinity and high specificity	Although both antibodies and aptamers offer high binding affinities and specificity, aptamers can resist denaturation due to pH changes, unlike antibodies whose binding efficiency may be affected.
Nucleic acids	Moderate binding affinity and moderate specificity	High binding affinity and high specificity	Aptamer production can be controlled to produce highly specific and selective aptamers. Additionally, aptamers can be synthetically modified to allow covalent immobilization and are more thermally stable and pH-tolerant.
Pathogens	High binding affinity and high specificity	High binding affinity and high specificity	Aptamers can detect whole-celled pathogens and induce conformational changes when synthesized as biorecognition elements, enabling real-time detection.
Disease biomarker	High binding affinity and high specificity	High binding affinity and high specificity	Aptamers are preferred as antibody-based detection often results in high background noise, while aptamer-based assays offer cleaner results.

like surface plasmon resonance and surface-enhanced Raman spectroscopy to capture these elusive targets. The ability of aptamers to undergo conformational changes upon target binding significantly amplifies their signal [66, 170]. Aptamer-based biosensors have demonstrated significant success in detecting small molecules such as antibiotics, hormones, and toxins. A study by [109] used a DNA aptamer to detect kanamycin and neomycin with detection limits as low as 0.89 ng/mL and 1.55 ng/mL, respectively. Such biosensors are critical for monitoring food safety and environmental contamination.

4.2 Protein and enzyme detection

Proteins and enzymes, crucial in diagnostics and pharmaceuticals, require precise detection. Aptamer-based biosensors, particularly using nanowire FETs, enhance sensitivity to proteins such as dopamine. Aptamers' small size allows them to bring bound proteins closer to the sensor's surface, improving the detection signal. Integrating aptamers into gold nanoparticles or other materials also amplifies the signal for early cancer detection [66].

4.3 Detection of nucleic acids

Nucleic acid detection benefits from the aptamer's ability to identify specific sequences with high precision. Optical biosensors employing aptamers can quickly and accurately detect genetic materials. Combining aptamers with advanced amplification and transduction methods enhances the detection speed and reliability for applications like pathogen identification and genetic analysis (Fig 8).

4.4 Detection of pathogens and microorganisms

Aptamer-based optical biosensors excel in pathogen detection due to their rapid response and specificity. The combination of aptamer capture probes and optical transducers enables the detection of bacteria and viruses with high sensitivity. Their ability to distinguish between pathogen strains supports improved public health monitoring and disease management [66]. Aptamer-based optical biosensors have been applied extensively in detecting bacterial and viral pathogens. For instance, aptamers specific to *Escherichia coli* and *Staphylococcus aureus* were used to develop a dual-analyte SPR biosensor, achieving detection limits as low as 10^5 cfu/mL and 10^6 cfu/mL, respectively [113]. These sensors are capable of detecting pathogens in real-time, offering a rapid, label-free method for disease diagnostics.

4.5 Disease biomarker detection

Disease biomarkers can be detected more effectively with aptamer-based biosensors, which identify and quantify markers indicative of physiological or pathological states. Techniques like multiplexing and signal amplification make these sensors suitable for early diagnosis and personalized medicine. The flexibility of aptamer sequences allows comprehensive profiling across different diseases.

4.6 Advancements in aptamer-based sensor design and signal amplification

Recent advancements in sensor design include identifying novel aptamer sequences via SELEX, allowing more precise target recognition. Techniques like fluorescence-based aptamers and nanoparticle amplification help develop highly sensitive sensors. Silicon nanowire-based FETs offer hypersensitive detection of biomolecules. Nanoparticle-based systems integrated with aptamers further amplify signals [66, 170].

4.7 Protein and enzyme detection

The high binding specificity of aptamers makes them suitable for detecting proteins such as thrombin and enzymes like lysozyme. An aptamer-based sensor for thrombin detection achieved a linear range of 5–20 nM with an LOD of 0.7 nM [111]. These sensors provide valuable tools for clinical diagnostics, particularly in detecting blood coagulation disorders.

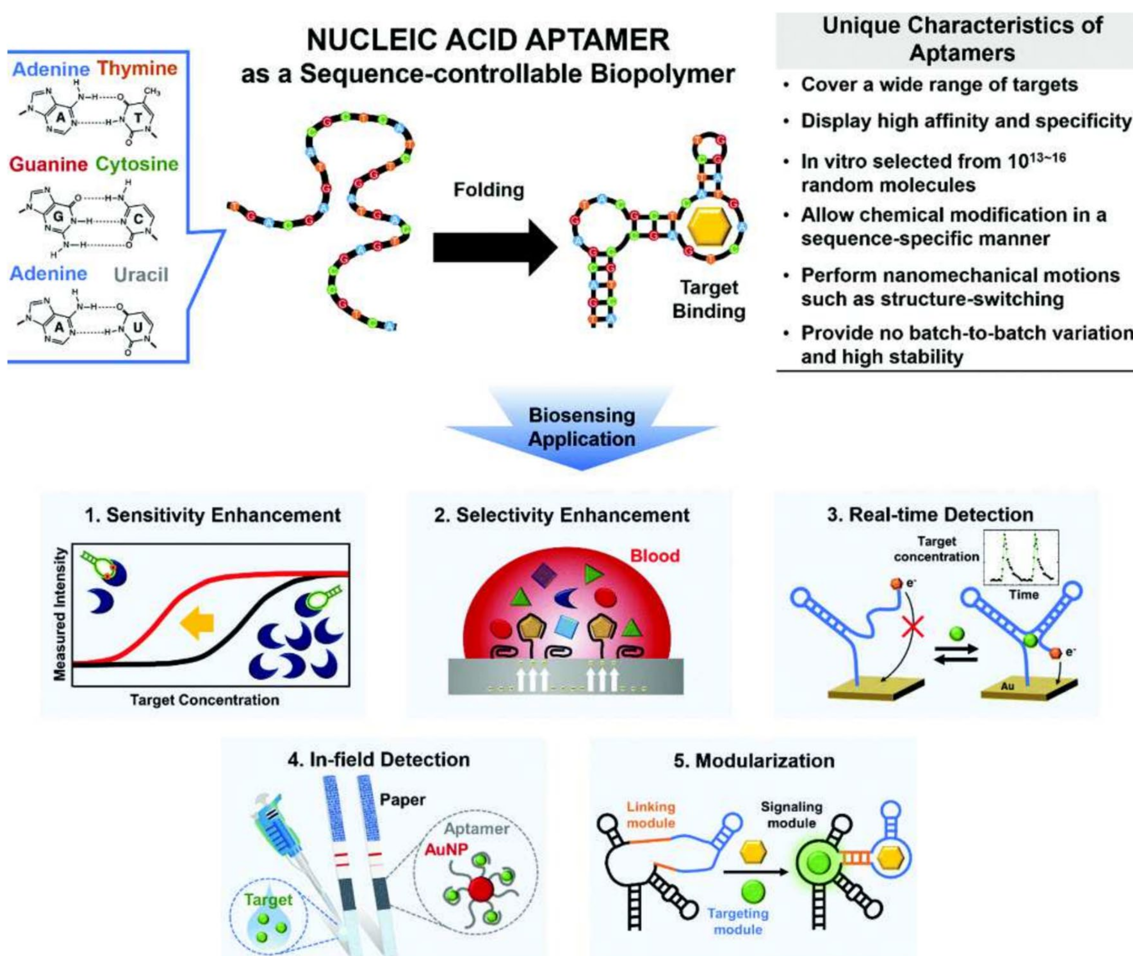

Fig. 8 Nucleic acid aptamers, through specific base pairing, fold into well-defined 3D structures for effective molecular recognition. These synthetic biopolymers offer the potential for the next generation of biosensors by overcoming the constraints of traditional sensors. This review highlights technical advancements in aptamer-based biosensors, such as heightened sensitivity, improved selectivity, and real-time detection applications. These biosensors also provide modular adaptability, paving the way for new applications in molecular diagnostics and field detection. Taken from [66]

4.8 Cellular detection and analysis

Aptamer-based optical biosensors have also found applications in cellular detection. For instance, a biosensor designed to detect MCF-7 breast cancer cells using folic acid-modified magnetic nanoparticles achieved a detection range of 500–10,000 cells/mL [122]. These sensors enable non-invasive diagnostics and facilitate the study of cell behavior, helping to advance cancer research.

4.9 Multiplexed biosensing and point-of-care diagnostics

Recent advancements have focused on multiplexed biosensing, where multiple aptamers are integrated within a single platform to detect several analytes simultaneously. This is particularly valuable for point-of-care diagnostics, where rapid and accurate detection is critical. A dual-aptamer biosensor targeting thrombin demonstrated a broad detection range from 0.1–2 aM, enabling ultra-sensitive diagnostics [120].

4.10 Aptamer integration with emerging technologies

Aptamers are increasingly being integrated with emerging technologies such as quantum dots and photonic crystals to enhance optical biosensors. A biosensor employing near-infrared quantum dots to detect C-reactive protein achieved an impressive LOD of 5 fg/mL [124]. These hybrid systems combine the advantages of aptamers with the unique properties of nanomaterials, providing highly sensitive biosensing platforms.

4.11 Cancer biomarker detection

Optical biosensors using aptamers as recognition elements have been employed to detect biomarkers related to cancer. For example, an aptamer-based biosensor targeting the B-type natriuretic peptide (BNP) achieved a LOD of 1 aM, making it highly effective for early detection [121]. This level of sensitivity allows the detection of cancer at early stages, improving patient outcomes by enabling timely interventions.applications [100].

5 Applications of antibodies in optical biosensing

Optical biosensors rely on detecting alterations in optical traits due to the presence of an analyte, like changes in absorption, reflectance, emission, or interferometric patterns. These alterations are picked up by a photodetector [171]. The surface plasmon resonance (SPR) optical biosensors are the most prevalent type, known for their specificity, sensitivity, and cost-effectiveness. They excel at delivering detailed information about a sample, such as kinetic behavior, concentration, and molecular interactions, without being affected by electrical or magnetic interference [170]. Their high sensitivity enables them to detect analytes even at incredibly low concentrations like attomolar levels. Among various receptors, antibodies are highly effective and selective in binding to their specific antigens. These proteins are produced by B-lymphocytes, specialized cells of the immune system. Antibody molecules consist of four polypeptides arranged in a "Y" shape, comprising two heavy chains and two light chains. The variability in amino acid sequences at the tips of the "Y" provides antibodies with their unique specificity for binding antigens. Antibody-based sensors are valuable for the quick and sensitive analysis of pathogens and their associated toxins [172].

In the realm of diagnostics, biomolecular sensors are crucial, combining biological components like capture probes or enzymes with physical elements such as optical or electrical systems. Antibodies, with their epitope-binding recognition sites, play a central role in identifying pathogens like viruses. Fluorescent probes, enzymes, and nanomaterials can be attached to antibodies for signal enhancement in detection systems. Immunosensors, a subset of biosensors, utilize antibody-based biorecognition elements. They work by generating a signal which has an inverse proportionality relationship to the concentration of antigens and antibodies in the sample, which a transducer then translates. Antibodies can be customized to bind to different target molecules, including ones with small molecular sizes [173]. When integrated into optical sensors, antibodies enhance the robustness, sensitivity, and speed of analysis, making them indispensable tools in modern diagnostics (Fig. 9).

5.1 Detection of small molecules (e.g., toxins, drugs)

Small molecules refer to organic compounds with low molecular weights, typically under 1000 Da. They encompass a diverse range of natural or synthetic chemicals that are relevant in biology, pharmacology, and environmental studies. Detecting and quantifying these molecules is crucial across disciplines. Antibodies are widely used in SPR sensors due to their versatility and broad specificity. However, other options like molecularly imprinted polymers (MIPs) and aptamers are being explored for small molecule detection. Recombinant antibodies have been successfully employed in SPR biosensors for detecting small molecules like mycotoxins, achieving detection limits below regulatory thresholds [172]. In a study by Tomassetti et al., the researchers conducted a comparison between an SPR immunosensor for ampicillin and a competitive amperometric immunosensor. While the amperometric method showed better sensitivity and a wider dynamic range, the SPR sensor exhibited greater selectivity, speed, and simplicity in analysis, especially within the concentration range of 10-6 M to 10-2 M [172]. Additionally, localized surface plasmon resonance (LSPR) sensors have been

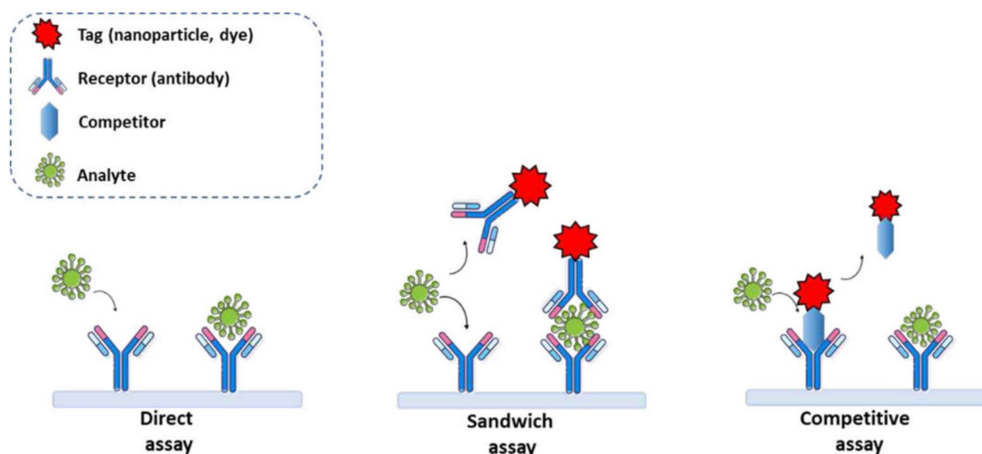

Fig. 9 Depiction of three assays employed in affinity-based sensors. In a direct test, the signal is produced by the analyte itself. A sandwich assay employs a tag or detection probe to generate a signal upon binding of an analyte. In a competitive test, the presence of an analyte prevents the interaction between the receptors and a labeled competitor that is detected

developed using core-shell nanosensors composed of polystyrene nanospheres as the core and a thermally deposited gold layer as the shell [174]. Biofunctionalization of these nanosensors with atrazine-specific antibodies enabled direct detection of atrazine at a concentration of 10 ng/mL [175, 176].

5.2 Protein and enzyme detection

Proteins are vital components of living organisms, playing roles in numerous cellular processes like metabolic reactions, DNA replication, stimulus response, cellular structure maintenance, and molecule transport. Detecting and identifying proteins quickly and affordably is crucial in fields like biomedicine and food industry. Over time, various protein detection methods have been developed, each with its own strengths and weaknesses. For instance, immunoblotting, while highly sensitive and specific, is costly and technically demanding. Immunohistochemistry, on the other hand, is used for qualitative protein analysis but may suffer from bias, low sensitivity, and specificity [177]. Optical fiber biosensors have seen remarkable advancement in protein detection due to their high sensitivity and selectivity. Among these biosensors, label and label-free techniques are commonly used. Proteins absorb light strongly in the wavelength range from 280 nm - 260 nm (ultraviolet). Researchers like Sai et al. utilized this absorption property to develop fiber-optic biosensors for protein detection with high sensitivity [164]. Leung et al. utilized a 1550 nm laser and a fiber-optic biosensor customized with antibodies to monitor the binding of proteins, achieving impressive sensitivity down to 10 fg/mL [178]. Gold nanoparticles (AuNPs) are popular for their extinction property, selectively absorbing evanescent waves near fiber surfaces. Combining AuNPs with sensitized fiber platforms enhances absorption, as demonstrated by Li et al for alphafeto protein detection [179]. In SPR-based protein detection, immobilizing biomolecule receptors on metal thin-films is critical. The use of sulfhydryl (-SH) groups facilitates biomolecule immobilization on gold films due to strong Au-S bonds. Alternatively, intermediate protein materials like protein A or protein G can bridge Au films and proteins for immobilization, improving stability and molecular recognition [180].

5.3 Detection of nucleic acids

Nucleic Acid (NA) analysis for diagnostics has gained significant attention due to their potential as biomarkers for early disease detection, especially in infectious diseases and cancer. Plasmonic-based biosensors, SPR-based biosensors, are widely used for NA analysis due to their advanced technology and sensitivity. Detecting NA poses challenges as they are usually present in low concentrations and linked with subtle gene expression changes. For instance, miRNA analysis requires sensitivity ranging from nanomolar to attomolar concentrations. Achieving the necessary sensitivity involves using highly sensitive biosensor transducers and amplification techniques, such as PCR-based procedures, or signal enhancers, such as DNA/RNA binding proteins or nanomaterials. Li et al, demonstrated dual amplification in an SPR sensor using a two-layer GO-AuNPs composite. The bottom layer immobilized SH-DNA probes on nanoparticles, making the sensor functional [179]. In the second step, target miRNA combined with probes that were already attached and interacted with DNA-functionalized GO-AuNPs mixtures, which improved sensor signals. This two-layer method greatly increased the LOD (0.1 fM) for miRNA-141 detection from cancer cell lines compared to single-layer substrates, showing that it is very good at finding things [179, 180].

5.4 Pathogen detection (e.g., bacteria, viruses)

Pathogens are foreign antigens with harmful effects, such as producing toxins, penetrating tissues, and immunosuppressing hosts. Contagious pathogens like those causing bacterial urinary tract infections, malaria, influenza, dengue, HIV, and SARS-CoV-2 can transmit from person to person before symptoms appear. Recent studies focus on developing novel diagnostic tools with pathogen binding mechanisms, like antigen-antibody interactions, to enhance sensitivity and selectivity. Plasmonic-based biosensors, including SPR, offer advanced detection capabilities with reduced costs and increased throughput. These biosensors detect pathogens through various plasmonic phenomena, such as SPR, localized SPR, and surface-enhanced techniques. SPR-based sensing is particularly promising for rapid and sensitive pathogen detection, replacing older diagnostic methods [173, 181]. These biosensors identify specific target biomarkers associated with particular pathogens using an immobilized sensing element called a bioreceptor. This bioreceptor, which can be a monoclonal antibody, RNA, DNA, glycan, lectin, enzyme, tissue, or whole cell, plays a critical role in ensuring high sensitivity and selectivity in biomarker detection. Its biochemical properties enable precise recognition of the biomarker while preventing interference from other microorganisms or molecules in the sample. The specific biochemical interaction between the biomarker and bioreceptor is then converted into a measurable signal by the transducer. Bong et al. designed an Au-based plasmonic biosensor sensor for SARS-CoV-2 diagnosis. By chemically attaching antibodies to a gold chip sensor, they were able to find serum isolates at a very low level (1.02 pM). The sensor demonstrated exceptional selectivity for coronavirus over other viruses like influenza, providing rapid and accurate results ideal for early disease detection [182].

5.5 Advancements in antibody-based sensor design and signal amplification

Optical biosensors offer high sensitivity, selectivity, and the potential for swift disease diagnosis. Challenges such as sample preparation, detection time, and real-time sensing can hinder early disease detection. However, optical biosensors, with their improved selectivity, superior signal-to-noise ratios, and minimal sample requirements, have emerged as a pivotal tool for early disease diagnosis in recent times. Constant modifications of the biorecognition receptor using different strategies have been made to increase their sensitivity. Site-specific covalent binding of an antibody to a transducer is essential not only for good sensitivity but also for reproducibility. Site-oriented antibody binding strategies have been utilized to enhance the sensitivity of electrochemical immunosensors. One big benefit of site-directed conjugation is that it might increase the ability of antigens to bind, which can make biomarker detection more sensitive and stable. It is possible to immobilize antibodies in a site-directed way by targeting different functional groups on them, such as sulfhydryl groups, carbohydrate groups (glycan conjugation), and the nucleotide-binding site (NBS). A lot of research has been done on the NBS, which is found in the area that stays the same between the variable regions of the light and heavy chains of Fab domains in antibodies that bind to IBA (indole-3-butyric acid). A special way of binding that involves using UV light (254 nm) to crosslink IBA to an NBS has been shown to improve sensitivity without changing the structure or function of the antibody. Nanomaterials play a crucial role in signal amplification due to their small controllable size and quantum effects. These attributes aid in enhancing signals when in direct contact with the biorecognition element interacting with the analyte of interest. Nanomaterials, particularly when conjugated with antibodies in the correct orientation, significantly influence sensitivity and reproducibility. By increasing current yield, they make an interface that can sense changes in the physical world caused by biochemical interactions. These changes are then turned into signals that can be picked up. Studies by Donghai Lin and colleagues highlight that orienting antibodies improves sensitivity, with nanoparticle-based methods showing a synergistic effect in sensitivity enhancement. Nanomaterials' distinct chemical and electrical properties also contribute to developing advanced sensing devices with heightened sensitivity and specificity. Various nanomaterials, including metals, carbon materials, polymeric nanocomposites, and semiconducting materials, have been explored as transducer materials in this context such as the system shown in Fig. 10 [98].

The differences in sensing performance between various types of nanoparticles are demonstrated in Fig. 11. The study compares the changes in SPR response at a fixed thrombin concentration of 1 fM when using anti-thrombin nanoparticle conjugates-nanocages, nanorods, and quasi-spherical particles [119]. Notably, the nanocage-conjugate injection induced minimal changes in the SPR signal, whereas the quasi-spherical particles produced a response more

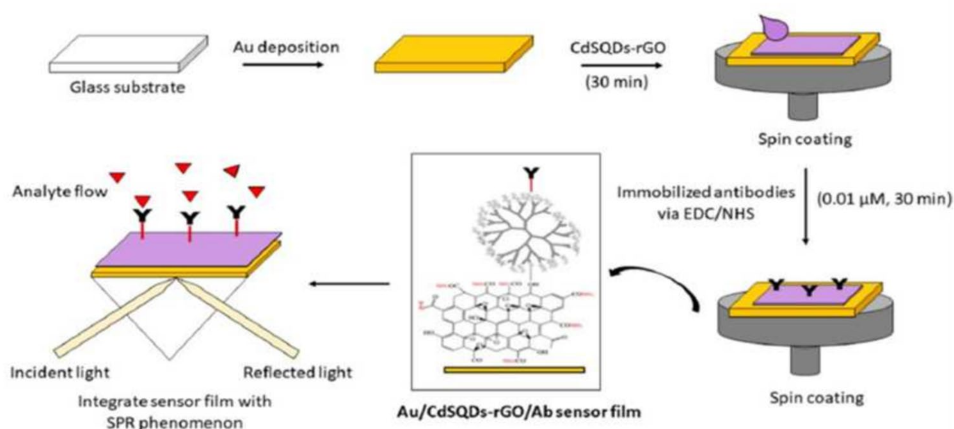

Fig. 10 Diagram illustrating the sequential process for creating a sensor film The material consists of quantum dots made of gold and cadmium sulfide, which are combined with reduced graphene oxide and antibodies (Au/CdSQDs-rGO/Ab) [98]

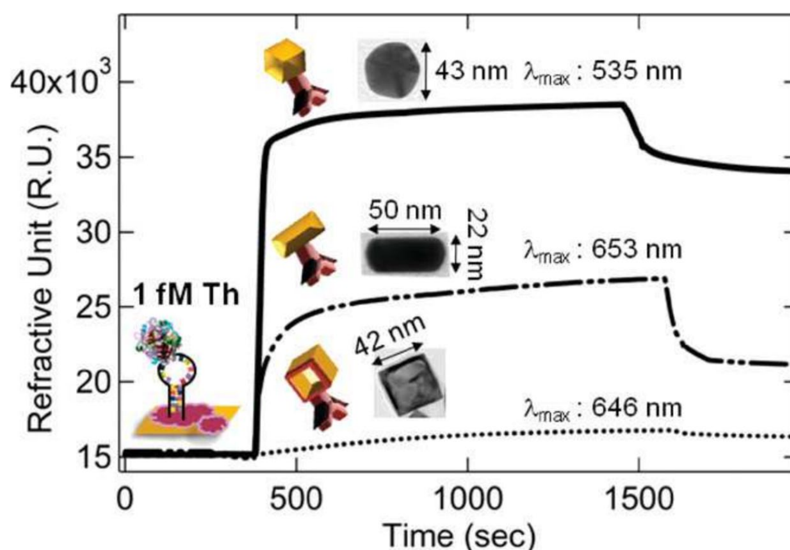

Fig. 11 Gold nanoparticles (AuNPs) used in a sandwich SPR biosensor for thrombin detection, demonstrating enhanced sensitivity. Adapted from [119] with permission

than double that of the nanorod samples when compared under identical buffer-only conditions. The experimental design ensured uniform functionalization across all nanoparticle types and optimized aptamer SPR chips to minimize nonspecific adsorption, yielding reproducible results [119]. Antibody attachment efficiency and fractional surface coverage were optimized to minimize performance variation among nanoparticle conjugates. A uniform spacing between the nanoparticles and the gold film surface was maintained, given that previous research has shown the importance of separation distance in nanoparticle-enhanced SPR responses. The observed signal enhancement differences among nanoparticle types arise from their distinct effects on the real and imaginary components of the refractive index at the chip-solution interface. The real component is influenced by the high material density of the nanoparticles, while the imaginary component is affected by near-field plasmonic coupling between the gold film and nanoparticle. The extinction spectra suggest stronger plasmonic coupling for nanorods and nanocages, but these effects are influenced by the red-shift in the local SPR profile caused by the proximity of the nanoparticles to the gold surface. This red-shift, which can be as large as 100 nm, emphasizes the importance of the surface-particle separation distance. The quasi-spherical nanoparticles demonstrated superior sensing performance despite weaker overlap with the instrument's excitation wavelength compared to nanocages. This enhanced performance can be attributed to their higher material density and greater volume, which induce a larger change in the real component of the refractive index. In contrast, the lower density and smaller average volume of nanorods contribute to their reduced sensing performance on a 1:1 comparison basis. With each nanoparticle type having at least one dimension in the range of 40–50 nm, it is reasonable to conclude that differences in surface area coverage are negligible [119].

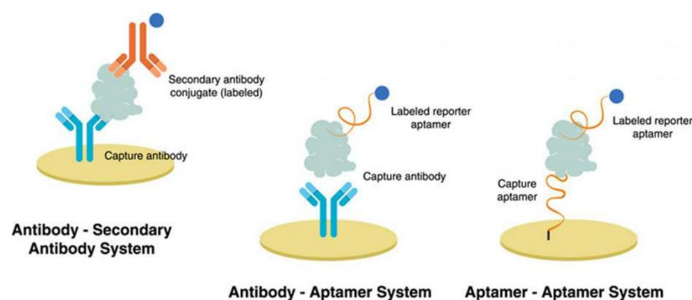

Fig. 12 The immobilization procedures should not impede the biological activity of the bioreceptor towards the target. Crucially, it should optimize the exposure of the binding sites to the target analyte [183]

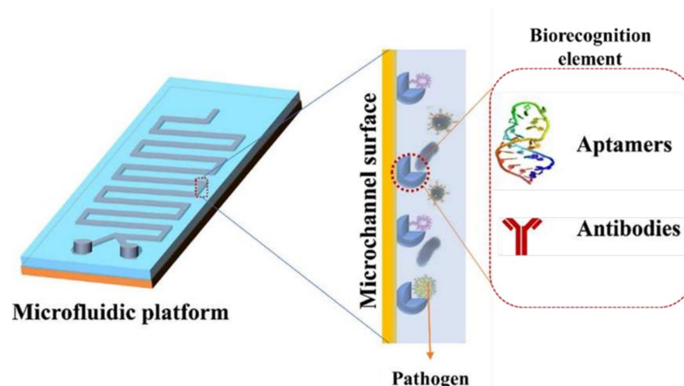

Fig. 13 A schematic representation of a microfluidic platform, functionalized with biorecognition elements such as antibodies or aptamers

6 Integration of aptamers and antibodies into diagnostic platforms

Recent reviews suggest that antibody- and aptamer-based biosensors show similar performance levels, particularly in terms of sensitivity and selectivity. However, their effectiveness is heavily influenced by how they are immobilized onto the transducer and the chosen detection mode. Various techniques, such as supramolecular interactions, covalent chemical coupling, physicosorption or chemosorption, and copolymerization, can be employed to attach antibodies, aptamers, proteins, and other bioreceptors onto biosensor surfaces. Depending on the detection method, the substrate can be used to immobilize either the antibody, aptamer, or target antigen. Effective immobilization techniques facilitate the establishment of the bioreceptor-biomarker complex on the surface of the substrate and stimulate the creation of signals (Fig. 12). The immobilization procedures should not impede bioreceptor biological activity towards the target. The exposure of the binding sites to the target analyte should be optimized [183].

6.1 Microfluidic and lab-on-a-chip devices

Microfluidics technology has revolutionized detection applications in recent years due to its numerous advantages, including portability, miniaturization, automation, multichannel sample detection, minimal handling of hazardous substances, and cost-effectiveness. One of the key strengths of microfluidics is its ability to create a controlled microenvironment that efficiently drives and regulates microfluidic flow within microchannels, leading to enhanced detection sensitivity (Fig. 13). Furthermore, microfluidic systems integrate all analytical processes, such as sample preparation, reactions, separations, and detection, into a single microfluidic chip, making them highly suitable for field testing applications [184–187].

Antibodies are commonly immobilized on electrode setups and integrated with microfluidic technologies to allow for pathogen detection. Microfluidic biosensors often incorporate immunomagnetic separation (IMS) alongside magnetic nanoparticles (MNPs) due to their advantages such as large specific surface area and uniform distribution, enabling specific isolation and efficient concentration of pathogens. Park et al. developed a plastic-based 3D magnetic microfluidic pre-concentrator that can selectively pre-concentrate *E.coli* O157:H7 to 100 µL at a 700-fold ratio

within an hour, enabling detection as low as 10 CFU/mL in blood when combined with an ATP photometer [173]. Adding aptamers to sensing platforms is becoming more popular as a way to improve the precision in analyte detection, especially LOC technologies, POC diagnostic devices, and personal medicine. Aptamer-based sensors integrated with LOC devices show promising results, addressing pressing healthcare challenges [188]. Microfluidics, sometimes referred to as miniature total analysis system (μTAS) or lab-on-a-chip (LOC) technology, provides numerous benefits in the field of biosensing. Microfluidic-based biosensors allow for real-time detection, automated measurements, smaller sample sizes and faster detection times, higher throughput, portability, and disposal, and better sensitivity due to the high surface-to-volume ratio. Aptamers outperform antibodies when integrated into microfluidic technologies due to their enhanced suitability for fluorescent labeling and prolonged stability across diverse environments [189, 190]. Aptamers have been successfully employed as affinity probes in microfluidic chips for various applications, such as electrophoretic separation for thrombin analysis and miniaturized affinity chromatography for detecting hepatitis C RNA polymerase at low concentrations. Also, label-free aptamer biosensors have been created to selectively detect vasopressin on microfluidic platforms. This shows that they could be used to make portable point-of-care (POC) diagnostic devices. Where carbon nanotubes (CNTs) were deposited between two lithographically patterned gold electrodes on a silicon wafer, with a 10 μm gap. These CNTs were then functionalised using amine-terminated aptamers via carbodiimide and N-hydroxysuccinimide (EDC/NHS) chemistry. After that, the aptamer-changed setup was put together with a polydimethylsiloxane (PDMS) microfluidic channel to make it easier for a vasopressin solution to flow. The detection mechanism involved measuring the current changes before and after vasopressin binding [191, 192]. In recent years, microfluidic-integrated optical biosensors have demonstrated significant potential for improving biosensing performance. These systems enable precise fluid control, reduce sample volumes, and provide rapid detection, making them essential in the development of compact diagnostic tools. One recent study by Granata et al. [193] introduced a microfluidic-integrated plasmonic sensing platform designed for selective detection of anti-folic acid (A-FA) using clusters of gold nanoparticles (NPs) [193]. This device enhances surface plasmon resonance (SPR) sensitivity by ensuring uniform delivery of reagents and functionalization of the plasmonic surface, addressing the challenge of low specificity in complex biological matrices. The study optimized the microfluidic chamber to eliminate dead zones, ensuring consistent reagent exposure across the plasmonic surface. Additionally, the system leverages both surface-enhanced Raman spectroscopy (SERS) and fluorescence capabilities, enhancing the electromagnetic field for detailed molecular detection. The ligand-receptor interaction between the folic acid-cysteine complex and A-FA ensures selective biomarker capture. The device demonstrated optimal performance at a flow rate of 10 μl/min, balancing sensitivity and reagent use, making it a promising platform for cancer biomarker detection with minimal sample volumes. Furthermore, other studies highlight the potential of microfluidics for various applications. For instance, one work explores the integration of SPR sensors for environmental monitoring, demonstrating enhanced detection sensitivity through nanoparticle amplification. Another recent study developed a hybrid microfluidic device capable of integrating multiple sensing modalities for multiplexed detection, offering a significant improvement in diagnostic performance. Such advancements exemplify the trend towards lab-on-a-chip platforms that combine multiple sensing approaches to improve precision and throughput.These developments underscore the role of microfluidic technology in advancing the field of optical biosensing, enabling high-performance, compact diagnostic solutions suitable for point-of-care and environmental applications.

Early and precise detection of tumors significantly improves treatment outcomes. Microfluidic-based technologies offer promising solutions for cancer diagnosis; however, the laminar flow characteristic of microfluidic channels often limits mass transfer, reducing biosensing efficiency and sensitivity. To address this issue, Li et al. (2022) developed a novel liquid biopsy chip embedded with antibody-conjugated microbeads [194]. The inclusion of microbeads enhances the contact surface area available for immunoaffinity reactions, thereby amplifying fluorescent signals and improving both sensitivity and efficiency.The device operates with minimal sample volume requirements (20–50 μ L) and achieves a low LOD of 0.1 ng/mL. With rapid detection times ranging from 55 to 75 min, the platform provides a fast, continuous method for biomarker analysis. The clinical utility of the system was validated using plasma samples from 15 breast cancer patients and 5 non-cancer controls. The chip detected two key biomarkers: carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3). Both biomarkers effectively differentiated cancer patients from non-cancer controls. Furthermore, Receiver Operator Characteristic (ROC) curve analysis demonstrated that the combined assessment of CEA and CA15-3 yields high sensitivity and specificity, confirming the reliability of this approach for early cancer diagnosis. This microfluidic chip offers a new strategy for rapid and precise diagnosis of cancer and potentially other diseases.

Plasmonic colorimetric biosensors have garnered increasing attention due to their cost-effectiveness, rapid responsiveness, and simplicity compared to conventional laboratory techniques [38]. These sensors offer potential for

high-throughput screening and easy-to-use procedures, making them ideal candidates for point-of-care (POC) devices. Despite these advantages, several challenges, such as complex fabrication processes, intricate biofunctionalization, and limited sensitivity, restrict their widespread adoption in industry [38]. Recent advancements in plasmonic nanomaterials continue to address these issues by improving the sensors' sensitivity, dynamic range, limit of detection (LOD), reliability, and specificity. The review by Acunzo et al. categorizes the latest developments into three main types of colorimetric biosensors:

- Platform-based: These include localized surface plasmon resonance (LSPR), coupled plasmon resonance, and surface lattice resonance, which rely on the interaction between light and nanostructured surfaces.
- Colloid aggregation-based: This category comprises label-based and label-free sensors that utilize changes in nanoparticle aggregation to detect analytes.
- Colloid non-aggregation-based: Methods such as nanozyme-catalyzed reactions, etching-based assays, and nanoparticle growth-based techniques fall into this category.

This review emphasizes how continuous improvements in plasmonic biosensors push the boundaries of sensitivity and specificity, further supporting research in developing reliable POC devices [38].

6.2 Wearable and implantable sensors

Wearable and implantable sensors play vital roles in personalized medicine, offering continuous monitoring for more effective disease management. Wearable sensors, such as smartwatches, are designed to be convenient, fashionable, easy to use, and noninvasive. They provide real-time data access and enable patient self-monitoring. However, they require compliance and maintenance to prevent loss or damage as patients can remove them at will [195]. On the other hand, implantable sensors are suitable for long-term monitoring, providing detailed insights into the body's internal environment. They offer real-time data collection to detect anomalies and complications early. However, implantable sensors are invasive and require surgical insertion, making them more expensive and posing risks such as infection or rejection by the body, unlike wearable sensors [196]. In essence, aptamers offer more stability than antibodies and can recover their structure after exposure to denaturing agents, making them suitable for continuous wearable monitoring with various regeneration strategies. They have shown promise in biosensors for insulin, particularly in diabetes management. Yoshida et al. utilized SELEX to isolate DNA aptamers against insulin, identifying IGA3 as a G-rich aptamer that forms a G-quadruplex with high affinity for insulin. They designed an enzyme system with IGA3 coupled to a thrombin-inhibiting aptamer, where insulin binding releases thrombin for activity measurement, correlating with insulin levels [197]. Subsequent studies used IGA3 in insulin biosensor development, such as Wu et al.'s electrochemical biosensor immobilizing IGA3 on a gold electrode. Insulin binding induced a conformational change detectable by electron transfer changes, achieving detection limits of 20 nmol/L. These biosensors are specific, selective, and hold potential for clinical applications [198]. Additionally, electrochemical biosensors based on the insulin-linked polymorphic region (ILPR) DNA sequence achieved low detection limits down to 50 nmol/L, enhancing the versatility of aptamer-based insulin biosensing [199]. Aptamer sensors provide excellent versatility in screening numerous indicators and medicines, making them highly promising for wearable drug monitoring, in comparison to enzyme-based electrochemical sensors and electrochemical immunosensors. Nevertheless, in order to fully exploit this potential, it is necessary to overcome other problems, such as improving the sensitivity of the signal, optimizing the methods used for screening aptamers, creating new redox probes, and attaining downsizing. A recent study by Jun-Chau Chien et al, introduced a miniaturized wireless implantable system powered by ultrasound. This system communicates with an electrochemical "surface" sensor to detect kanamycin (an aminoglycoside antibiotic) and doxorubicin (a chemotherapeutic drug) aptamers for therapeutic drug monitoring. These sensors can operate directly in the bloodstream or in the perivascular extracellular matrix near tumor sites [200].

6.3 Point-of-care diagnostics

Accurate and scalable POC diagnostics devices for pathogens could revolutionize diagnostics by enabling community-based testing outside traditional lab settings. These tests offer the potential to shorten the time for actionable results, aiding in early COVID-19 detection, optimizing isolation resources, implementing infection control measures effectively, and facilitating patient recruitment into treatment trials. Lateral flow assays (LFAs), a type of POC diagnostic test, are particularly suited for resource-limited settings, aligning with WHO's REASSURED criteria (Real-time connectivity, Ease of

specimen collection, Affordable, Sensitive, Specific, User-friendly, Robust and rapid, Equipment-free, Deliverable) [201]. LFAs utilize antibodies as recognition elements and have gained traction as various companies develop lateral flow devices for rapid infectious disease diagnosis.

Chih-Hung et al did work where multiple bacteria-specific aptamers were identified using bacterial SELEX. These highly specific aptamers were then incorporated into a microchip-based assay capable of simultaneously detecting all three target bacterial species within 35 min. Unlike antibody-based analyses, this system operates without an external power source and offers advantages such as faster detection times and multiplexing capability [202]. Consequently, the NC-based microfluidic system developed in this study has the potential to serve as a valuable tool for diagnosing multiple nosocomial bacterial types, particularly in high-risk or high-infection areas like intensive care units.

7 High-throughput screening platforms

A primary objective is to create affordable diagnostics suitable for remote areas. On-chip immunoassays share similarities with standard LFIA, ELISA, or molecular diagnostics platforms, but microfluidic technologies simplify assays, allowing for multiplex analysis and high-throughput screening. On-chip nucleic acid analysis is particularly promising as it integrates various assay steps like cell lysis, nucleic acid purification, amplification, and detection. Current efforts in high-throughput screening diagnostics involve identifying new biomarkers, optimizing microfluidic design and materials, and utilizing biorecognition elements like antibodies or aptamers along with detector technologies and towards multiplex detection of several biomarkers [202]. Cost per test and the need for instrumentation are critical considerations. A novel approach involves using layered paper to create three-dimensional microfluidic devices, enabling fluid distribution and crossing streams without mixing. An example is a mobile electrochemical detector that can transmit results via mobile phones, crucial for diagnostics in resource-limited settings [203].

8 Role of nanomaterials in optical biosensor fabrication

Nanomaterials have emerged as essential components in the development of highly sensitive and selective optical biosensors. Their unique physical, chemical, and optical properties make them ideal for enhancing biosensing parameters such as sensitivity, specificity, detection range, and LOD. This section elaborates on the role of nanomaterials in improving biosensor performance, providing insights into the mechanisms by which they contribute to enhanced biosensing.

8.1 Sensitivity enhancement through plasmonic nanomaterials

Metallic nanostructures, such as gold and silver nanoparticles, exhibit LSPR, which significantly enhances the sensitivity of optical biosensors. The resonance phenomenon amplifies the local electromagnetic field, increasing the interaction between the analyte and the biorecognition element. This results in improved signal-to-noise ratios, facilitating the detection of biomolecules even at ultra-low concentrations [116].

8.2 Specificity and selectivity improvement

Functionalized nanomaterials, such as polydopamine-coated nanoparticles and graphene oxide (GO), offer enhanced specificity. These materials can be easily modified with biomolecules like antibodies, aptamers, and enzymes, enabling selective binding to target analytes. This functionalization reduces cross-reactivity and increases selectivity, essential for accurate biosensing in complex biological samples [118].

8.3 Broadening detection range and lowering LOD

Nanomaterials also play a critical role in expanding the detection range of biosensors. Dual nanomaterials, such as gold nanorods combined with quasi-spherical nanoparticles, enable multi-modal detection, covering a wider dynamic range. Moreover, the use of nanocages and quantum dots can lower the LOD by several orders of magnitude, making it possible to detect analytes in the femtomolar and attomolar ranges [119, 124].

8.4 Improved stability and reusability

Incorporating nanomaterials such as graphene oxide or magnetic nanoparticles enhances the mechanical stability and reusability of biosensors. These materials are resistant to environmental degradation and can support repeated analyte detection cycles without compromising performance. This not only improves cost-efficiency but also increases the sensor's operational lifespan [125].

8.5 Nanomaterials as signal transducers and amplifiers

Nanomaterials can act as transducers, converting biological recognition events into optical signals with high efficiency. In addition, they amplify signals by interacting with fluorescence, Raman scattering, or photonic crystal structures, making them useful for multiplexed and highly sensitive biosensing applications [100].

9 Challenges and limitations of antibodies and aptamers in optical biosensing

While antibodies offer high specificity and sensitivity, there are several challenges associated with their use in optical biosensing. Antibodies may exhibit cross-reactivity with structurally similar molecules, leading to false-positive results [204]. Ensuring the specificity of antibodies is crucial for accurate detection in complex biological samples. Antibodies can also be sensitive to environmental factors such as temperature, pH, and ionic strength, which can affect their stability and performance over time [47, 205–207]. Proper storage conditions and handling protocols are essential to maintain antibody integrity. Efficient immobilization of antibodies onto the sensor surface is critical for optimal performance. Inadequate immobilization can result in low binding capacity, reduced sensitivity, and increased nonspecific binding, affecting the accuracy and reliability of the assay [47]. The orientation of immobilized antibodies can impact their binding affinity and accessibility to target analytes. Maintaining the active conformation of antibodies during immobilization is crucial for maximizing binding efficiency and signal generation [47]. Regeneration of the sensor surface after analyte binding is necessary for repeated use of the biosensor. However, harsh regeneration conditions can lead to antibody denaturation or desorption, compromising sensor performance and reusability [208]. Production of high-quality antibodies can be expensive and time-consuming, particularly for custom or rare targets. Additionally, batch-to-batch variability and limited availability of specific antibodies may pose challenges for assay standardization and reproducibility [205]. Complex sample matrices, such as serum, plasma, or tissue extracts, can contain interfering substances that affect antibody binding and signal detection. Sample pretreatment or matrix-compatible assay formats may be required to mitigate matrix effects and improve assay performance [209]. These challenges are actively being addressed through advancements in nanomaterials, surface modification, and improved interface design.

Aptamers also come with a range of challenges. The SELEX process involves multiple rounds to obtain high-affinity aptamers, which can be laborious and time-consuming [66, 170]. Aptamers are generally more stable than antibodies but remain susceptible to degradation by nucleases or harsh environmental conditions. Modifying their structure chemically can improve stability [66, 170]. Efficient immobilization on sensor surfaces is essential for effective biosensing. The method varies by platform and requires optimization to ensure aptamers maintain their specificity [170]. Aptamers often change shape upon binding, affecting their optical properties and signal transduction. Understanding and managing these changes is crucial for accurate detection [66]. Despite their high specificity, aptamers can sometimes cross-react with structurally similar molecules. Rigorous validation and careful selection helps minimize false positives [66, 170]. Repeated regeneration of aptamer surfaces can lead to denaturation, reducing their reusability. Developing gentle regeneration protocols is necessary [66]. Production costs for custom aptamers, particularly for rare targets, can be high. Limited availability may also hinder their adoption in large-scale applications [66]. Incorporating aptamers into signal transduction systems like fluorescence or surface plasmon resonance while retaining high sensitivity and signal-to-noise ratio is technically challenging [66].

10 Future outlook

The future outlook on the use of antibodies and aptamers in optical biosensors is quite promising due to their increasing applications and improvements in sensing capabilities. Aptamers are single-stranded DNA or RNA molecules that are made chemically. They are better than antibodies in many biosensing applications because they are stable, specific, and can be used again and again. A study that looked at how well aptamers and antibodies worked in optical porous silicon

biosensors discovered that aptamer-based sensors were better at reusability and storage, while antibodies immobilized with a specific orientation showed similar detection rates as aptamers. Aptamers are thus positioned as advantageous alternatives for biosensing [126]. Meanwhile, advancements in optical biosensor technologies are allowing more sensitive, specific, and rapid detection, particularly in environmental monitoring. Optical biosensors leverage various mechanisms like fluorescence, luminescence, and Raman scattering to detect target analytes in real-time with minimal sample preparation. They integrate aptamers and antibodies as recognition elements, contributing to more precise pollutant detection and environmental monitoring [84]. These developments suggest that both antibodies and aptamers will continue to play a crucial role in biosensing. Antibodies will be improved for optimal orientation and specificity, while aptamers will expand their range of applications due to their higher stability, adaptability, and ease of synthesis. Optical biosensors will benefit from these advances, offering improved environmental monitoring, healthcare, and industrial diagnostics. Machine learning algorithms also contribute strongly to technological developments in the biosensing space [210].

11 Conclusion

Enhancing the biosensor's sensitivity is the main goal of biosensor development. Aptamers, in our opinion, are the way of the future for optical biosensing research. The COVID-19 pandemic was a significant shock to the world, and it soon became evident that the world was not equipped to handle such pandemics in an effective manner from a diagnostic standpoint. Thus, in order to be ready for another pandemic, it is imperative that new diesease detecting methods be created. The integration of antibodies and aptamers into optical biosensing platforms has significantly enhanced the sensitivity, selectivity, and versatility of detection methods in various fields including healthcare, environmental monitoring, and food safety. Through meticulous design and optimization, researchers have demonstrated the capability of these biorecognition elements to detect analytes with high specificity and sensitivity, often surpassing traditional sensing techniques. Moreover, the compatibility of antibodies and aptamers with various optical transduction methods such as surface plasmon resonance, fluorescence, and surface-enhanced Raman scattering underscores their potential for widespread application in biosensing. Looking ahead, further advancements in biorecognition element engineering, alongside innovative optical detection strategies, promise to usher in a new era of optical biosensing with unparalleled accuracy, speed, and multiplexing capabilities. As we continue to refine and expand our understanding of these technologies, the prospect of deploying robust antibody- and aptamer-based optical biosensors in real-world settings for rapid, reliable, and cost-effective detection of target analytes becomes increasingly tangible, offering transformative solutions to pressing societal and environmental challenges. This paper reviewed the application of both aptamers and antibodies in biosensing, highlighted challenges with both and highlighted a direction for future work. The hope is that it opens up avenues for the development of more sensitive biosensors. In conclusion, optical biosensing technologies, particularly those based on LSPR, represent a promising approach for next-generation biosensing solutions. By identifying the gaps in current technologies and proposing future research directions, this review aims to guide the development of more reliable, sensitive, and versatile biosensors that meet the demands of modern diagnostic and analytical applications.

Author contributions Kelvin Mpofu, Sipho Chauke and Lungile Thwala contributed to the writing and review of this work. Patience Mthunzi-Kufa contributed to the review of the work.

Funding The authors acknowledge the Council for Scientific and Industrial Research (CSIR) and the Department of Science and Innovation (DSI) for the grant of funding for this research. K.M. was also supported by CSIR's Young Researchers Establishment Fund (YREF) the South African Quantum Technology Initiative (SAQuTi) and South African Medical Research Council (SAMRC).

Availability of data and materials This declaration is not applicable.

Declarations

Ethical approval and consent to participate This declaration is not applicable.

Competing interests The authors declare that they have no Competing interests.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You

do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Levitt AM, Khan AS, Hughes JM. Emerging and re-emerging pathogens and diseases. Infect Dis. 2010. https://doi.org/10.1016/B978-0-323-04579-7.00004-6.
2. Menon S, Mathew MR, Sam S, Keerthi K, Kumar KG. Recent advances and challenges in electrochemical biosensors for emerging and re-emerging infectious diseases. J Electroanal Chem. 2020;878: 114596.
3. Srinivasan B, Tung S. Development and applications of portable biosensors. J Lab Autom. 2015;20(4):365–89.
4. Bhatia D, Paul S, Acharjee T, Ramachairy SS. Biosensors and their widespread impact on human health. Sens Int. 2024;5: 100257.
5. Chadha U, Bhardwaj P, Agarwal R, Rawat P, Agarwal R, Gupta I, Panjwani M, Singh S, Ahuja C, Selvaraj SK, et al. Recent progress and growth in biosensors technology: a critical review. J Ind Eng Chem. 2022;109:21–51.
6. Walper SA, Lasarte Aragoneés G, Sapsford KE, Brown III CW, Rowland CE, Breger JC, Medintz IL. Detecting biothreat agents: from current diagnostics to developing sensor technologies. ACS Sens. 2018;3(10):1894–2024.
7. Kirsch J, Siltanen C, Zhou Q, Revzin A, Simonian A. Biosensor technology: recent advances in threat agent detection and medicine. Chem Soc Rev. 2013;42(22):8733–68.
8. Kulkarni MB, Ayachit NH, Aminabhavi TM. Recent advancements in nanobiosensors: current trends, challenges, applications, and future scope. Biosensors. 2022;12(10):892.
9. Kim K, Park CB. Femtomolar sensing of alzheimer's tau proteins by water oxidation-coupled photoelectrochemical platform. Biosens Bioelectron. 2020;154: 112075.
10. Citartan M, Gopinath SC, Tominaga J, Tang T-H. Label-free methods of reporting biomolecular interactions by optical biosensors. Analyst. 2013;138(13):3576–92.
11. Cunningham BT. Label-free optical biosensors: an introduction. Label-Free Biosens Techn Appl. 2009. https://doi.org/10.1017/CBO9780511626531.003.
12. Wang J, Ren Y, Zhang B. Application of microfluidics in biosensors. Advances in Microfluidic Technologies for Energy and Environmental Applications. 2020.
13. Chambers JP, Arulanandam BP, Matta LL, Weis A, Valdes JJ. Biosensor recognition elements. Curr Issues Mol Biol. 2008;10(1–2):1–12.
14. Xu J, Lee H. Anti-biofouling strategies for long-term continuous use of implantable biosensors. Chemosensors. 2020;8(3):66.
15. Naresh V, Lee N. A review on biosensors and recent development of nanostructured materials-enabled biosensors. Sensors. 2021;21(4):1109.
16. Chu C-J, Yeh C-S, Liao C-K, Tsai L-C, Huang C-M, Lin H-Y, Shyue J-J, Chen Y-T, Chen C-D. Improving nanowire sensing capability by electrical field alignment of surface probing molecules. Nano Lett. 2013;13(6):2564–9.
17. Schneider CS, Bhargav AG, Perez JG, Wadajkar AS, Winkles JA, Woodworth GF, Kim AJ. Surface plasmon resonance as a high throughput method to evaluate specific and non-specific binding of nanotherapeutics. J Control Release. 2015;219:331–44.
18. Banerjee S, Nilsen-Hamilton M. Aptamers for infectious disease diagnosis. In: E. Coli infections-importance of early diagnosis and efficient treatment. London: IntechOpen; 2019. p. 1–23.
19. Chandola C, Neerathilingam M. Aptamers for targeted delivery: current challenges and future opportunities. Role of novel drug delivery vehicles in nanobiomedicine, 2019;1–22.
20. Ilgu M, Fazlioglu R, Ozturk M, Ozsurekci Y, Nilsen-Hamilton M. Aptamers for diagnostics with applications for infectious diseases. Recent Adv Anal Chem. 2019. https://doi.org/10.5772/intechopen.84867.
21. Leija-Montoya AG, Benítez-Hess ML, Alvarez-Salas LM. Application of nucleic acid aptamers to viral detection and inhibition. Nucleic Acids-From Basic Aspects to Laboratory Tools, Edited by Marcelo L. Larramendy and Sonia Soloneski, 2016; 93–119.
22. Söylemez F, Türkseven ÇH. Aptamers and possible effects on neurodegeneration. In: Neuroprotection-new approaches and prospects. London: IntechOpen; 2019.
23. Sett A. Aptamers: magic bullet for theranostic applications. In: Theranostics-an old concept in new clothing. London: IntechOpen; 2020.
24. Jayasena SD. Aptamers: an emerging class of molecules that rival antibodies in diagnostics. Clin Chem. 1999;45(9):1628–50.
25. Tetin SY, Stroupe SD. Antibodies in diagnostic applications. Curr Pharm Biotechnol. 2004;5(1):9–16.
26. Siddiqui M. Monoclonal antibodies as diagnostics; an appraisal. Indian J Pharm Sci. 2010;72(1):12.
27. Trier NH, Houen G. Antibodies as diagnostic targets and as reagents for diagnostics. Basel: MDPI; 2020.
28. Weisser NE, Hall JC. Applications of single-chain variable fragment antibodies in therapeutics and diagnostics. Biotechnol Adv. 2009;27(4):502–20.
29. Borrebaeck CA. Antibodies in diagnostics-from immunoassays to protein chips. Immunol Today. 2000;21(8):379–82.
30. Torchynska TV. Physical reasons of emission varying in cdse/zns and cdsete/zns quantum dots at bioconjugation to antibodies. In: Quantum dots-theory and applications. London: IntechOpen; 2015.
31. Mehta J, Van Dorst B, Devriese L, Rouah-Martin L, Bekaert K, Somers K, Somers V, Scippo M-L, Blust R, Robbens R. The use of phages and aptamers as alternatives to antibodies in medical and food diagnostics. Biomed Eng Trends Res Technol. 2011. https://doi.org/10.5772/13584.
32. Leow CH, Cheng Q, Fischer K, McCarthy J. The development of single domain antibodies for diagnostic and therapeutic applications. In: Antibody engineering. London: IntechOpen; 2018. p. 175–204.

33. Mpofu K, Ombinda-Lemboumba S, Mthunzi-Kufa P, et al. Classical and quantum surface plasmon resonance biosensing. Int J Opt. 2023;2023:5538161.
34. Mpofu KT. Quantum plasmonic sensing with application to hiv research. PhD thesis, University of KwaZulu-Natal 2020.
35. Mpofu K, Lee C, Maguire G, Kruger H, Tame M. Experimental measurement of kinetic parameters using quantum plasmonic sensing. J Appl Phys. 2022;131(8): 084402.
36. Mpofu K, Lee C, Maguire G, Kruger H, Tame M. Measuring kinetic parameters using quantum plasmonic sensing. Phys Rev A. 2022;105(3): 032619.
37. Mpofu K, Mthunzi-Kufa P. Enhanced signal-to-noise ratio in quantum plasmonic image sensing including loss and varying photon number. Phys Scr. 2023;98: 115115.
38. Acunzo A, Scardapane E, De Luca M, Marra D, Velotta R, Minopoli A. Plasmonic nanomaterials for colorimetric biosensing: a review. Chemosensors. 2022;10(4):136.
39. Yadav AK, Basavegowda N, Shirin S, Raju S, Sekar R, Somu P, Uthappa U, Abdi G. Emerging trends of gold nanostructures for point-of-care biosensor-based detection of covid-19. Mol Biotechnol. 2024. https://doi.org/10.1007/s12033-024-01157-y.
40. Urmann K, Reich P, Walter J-G, Beckmann D, Segal E, Scheper T. Rapid and label-free detection of protein a by aptamer-tethered porous silicon nanostructures. J Biotechnol. 2017;257:171–7.
41. Minopoli A, Della Ventura B, Lenyk B, Gentile F, Tanner JA, Offenhäusser A, Mayer D, Velotta R. Ultrasensitive antibody-aptamer plasmonic biosensor for malaria biomarker detection in whole blood. Nat Commun. 2020;11(1):6134.
42. Arshavsky-Graham S, Heuer C, Jiang X, Segal E. Aptasensors versus immunosensors-which will prevail? Eng Life Sci. 2022;22(3–4):319–33.
43. Crivianu-Gaita V, Thompson M. Aptamers, antibody scfv, and antibody fab'fragments: an overview and comparison of three of the most versatile biosensor biorecognition elements. Biosens Bioelectron. 2016;85:32–45.
44. Chiu ML, Goulet DR, Teplyakov A, Gilliland GL. Antibody structure and function: the basis for engineering therapeutics. Antibodies. 2019;8(4):55.
45. Forthal DN. Microbiol Spectr. Functions of antibodies. 2014;2(4):10–1128.
46. Lipman NS, Jackson LR, Trudel LJ, Weis-Garcia F. Monoclonal versus polyclonal antibodies: distinguishing characteristics, applications, and information resources. ILAR J. 2005;46(3):258–68.
47. Welch NG, Scoble JA, Muir BW, Pigram PJ. Orientation and characterization of immobilized antibodies for improved immunoassays. Biointerphases. 2017. https://doi.org/10.1116/1.4978435.
48. Sharma S, Byrne H, O'Kennedy RJ. Antibodies and antibody-derived analytical biosensors. Essays Biochem. 2016;60(1):9–18.
49. Aslan Y, Atabay M, Chowdhury HK, Göktürk I, Saylan Y, Inci F. Aptamer-based point-of-care devices: emerging technologies and integration of computational methods. Biosensors. 2023;13(5):569.
50. Mascini M. Aptamers and their applications. Anal Bioanal Chem. 2008;390(4):987–8.
51. Patel DJ. Structural analysis of nucleic acid aptamers. Curr Opin Chem Biol. 1997;1(1):32–46.
52. Jarczewska M, Rębiś J, Górski Ł, Malinowska E. Development of dna aptamer-based sensor for electrochemical detection of c-reactive protein. Talanta. 2018;189:45–54.
53. Wu B, Jiang R, Wang Q, Huang J, Yang X, Wang K, Li W, Chen N, Li Q. Detection of c-reactive protein using nanoparticle-enhanced surface plasmon resonance using an aptamer-antibody sandwich assay. Chem Commun. 2016;52(17):3568–71.
54. Michaud M, Jourdan E, Villet A, Ravel A, Grosset C, Peyrin E. A dna aptamer as a new target-specific chiral selector for hplc. J Am Chem Soc. 2003;125(28):8672–9.
55. Paborsky LR, McCurdy SN, Griffin LC, Toole JJ, Leung L. The single-stranded dna aptamer-binding site of human thrombin. J Biol Chem. 1993;268(28):20808–11.
56. Yao J, Li S, Zhang L, Yang Y, Gopinath SC, Lakshmipriya T, Zhou Y. Aptamer-antibody dual probes on single-walled carbon nanotube bridged dielectrode: comparative analysis on human blood clotting factor. Int J Biol Macromol. 2020;151:1133–8.
57. Jenison RD, Gill SC, Pardi A, Polisky B. High-resolution molecular discrimination by rna. Science. 1994;263(5152):1425–9.
58. Jarczewska M, Wieczorek J, Malinowska E. Electrochemical studies on the binding of antibody-aptamer hybrid receptor layers to her2 protein. J Electrochem Soc. 2020;167(6): 067512.
59. Mehlhorn A, Rahimi P, Joseph Y. Aptamer-based biosensors for antibiotic detection: a review. Biosensors. 2018;8(2):54.
60. Shoji A, Kuwahara M, Ozaki H, Sawai H. Modified dna aptamer that binds the (r)-isomer of a thalidomide derivative with high enantioselectivity. J Am Chem Soc. 2007;129(5):1456–64.
61. Seo HB, Gu MB. Aptamer-based sandwich-type biosensors. J Biol Eng. 2017;11:1–7.
62. Hu X, Tang L, Zheng M, Liu J, Zhang Z, Li Z, Yang Q, Xiang S, Fang L, Ren Q, et al. Structure-guided designing pre-organization in bivalent aptamers. J Am Chem Soc. 2022;144(10):4507–14.
63. Zhang H, Zhou Y, Luo D, Liu J, Yang E, Yang G, Feng G, Chen Q, Wu L. Immunoassay-aptasensor for the determination of tumor-derived exosomes based on the combination of magnetic nanoparticles and hybridization chain reaction. RSC Adv. 2021;11(9):4983–90.
64. Gold L, Ayers D, Bertino J, Bock C, Bock A, Brody E, Carter J, Cunningham V, Dalby A, Eaton B et al. Aptamer-based multiplexed proteomic technology for biomarker discovery. Nature Precedings, 2010;1–1.
65. Zhou J, Rossi J. Aptamers as targeted therapeutics: current potential and challenges. Nat Rev Drug Discov. 2017;16(3):181–202.
66. Yoo H, Jo H, Oh SS. Detection and beyond: challenges and advances in aptamer-based biosensors. Mater Adv. 2020;1(8):2663–87.
67. Shu Y, Pi F, Sharma A, Rajabi M, Haque F, Shu D, Leggas M, Evers BM, Guo P. Stable rna nanoparticles as potential new generation drugs for cancer therapy. Adv Drug Deliv Rev. 2014;66:74–89.
68. González-Fernández E, de-los-Santos-Álvarez N, Miranda-Ordieres AJ, Lobo-Castañón MJ. Spr evaluation of binding kinetics and affinity study of modified rna aptamers towards small molecules. Talanta. 2012;99:767–73.
69. Lyu C, Khan IM, Wang Z. Capture-selex for aptamer selection: a short review. Talanta. 2021;229: 122274.
70. Neupane D, Stine KJ. Electrochemical sandwich assays for biomarkers incorporating aptamers, antibodies and nanomaterials for detection of specific protein biomarkers. Appl Sci. 2021;11(15):7087.
71. Svigelj R, Dossi N, Grazioli C, Toniolo R. based aptamer-antibody biosensor for gluten detection in a deep eutectic solvent (des). Anal Bioanal Chem. 2022;414:1–8.

72. Wu W, Liu L, Dai Z, Liu J, Yang S, Zhou L, Xiao X, Jiang C, Roy VA. Low-cost, disposable, flexible and highly reproducible screen printed sers substrates for the detection of various chemicals. Sci Rep. 2015;5(1):1–10.
73. Kim S, Lee HJ. Gold nanostar enhanced surface plasmon resonance detection of an antibiotic at attomolar concentrations via an aptamer-antibody sandwich assay. Anal Chem. 2017;89(12):6624–30.
74. Lee SH, Park YE, Lee JE, Lee HJ. A surface plasmon resonance biosensor in conjunction with a dna aptamer-antibody bioreceptor pair for heterogeneous nuclear ribonucleoprotein a1 concentrations in colorectal cancer plasma solutions. Biosens Bioelectron. 2020;154: 112065.
75. Zhu Y, Xu Z, Gao J, Ji W, Zhang J. An antibody-aptamer sandwich cathodic photoelectrochemical biosensor for the detection of progesterone. Biosens Bioelectron. 2020;160: 112210.
76. Chung S, Moon J-M, Choi J, Hwang H, Shim Y-B. Magnetic force assisted electrochemical sensor for the detection of thrombin with aptamer-antibody sandwich formation. Biosens Bioelectron. 2018;117:480–6.
77. Yunus MH, Yusof NA, Raston NHA, Noor SSM, Sulaiman Y, Abdullah J. A novel amperometric aptamer-antibody sandwich assay for the detection of tuberculosis with diazonium electrografted enhanced modified electrode. IEEE Sens J. 2021;21(20):22442–9.
78. Jarczewska M, Górski Ł, Malinowska E. Application of dna aptamers as sensing layers for electrochemical detection of potassium ions. Sens Actuators, B Chem. 2016;226:37–43.
79. Qiu Z, Shen Q, Jiang C, Yao L, Sun X, Li J, Duan C, Li R, Li X, Gopinath SC, et al. Alzheimer's disease determination by a dual probe on gold nanourchins and nanohorn hybrids. Int J Nanomed. 2021;16:2311–22.
80. Damborskỳ P, Švitel J, Katrlík J. Essays Biochem. Optical biosensors. 2016;60(1):91–100.
81. Zanchetta G, Lanfranco R, Giavazzi F, Bellini T, Buscaglia M. Emerging applications of label-free optical biosensors. Nanophotonics. 2017;6(4):627–45.
82. Chen C, Wang J. Optical biosensors: an exhaustive and comprehensive review. Analyst. 2020;145(5):1605–28.
83. Khansili N, Rattu G, Krishna PM. Label-free optical biosensors for food and biological sensor applications. Sens Actuators, B Chem. 2018;265:35–49.
84. Long F, Zhu A, Shi H. Recent advances in optical biosensors for environmental monitoring and early warning. Sensors. 2013;13(10):13928–48.
85. Schneider AFL, Hackenberger CPR. Fluorescent labelling in living cells. Curr Opin Biotechnol. 2017;48:61–8.
86. Lassen P, Carlsen L, Warwick P, Randall A, Zhao R. Radioactive labelling and characterisation of humic materials. Environ Int. 1994;20(1):127–34.
87. Rashidian M, Dozier JK, Distefano MD. Enzymatic labeling of proteins: techniques and approaches. Bioconjug Chem. 2013;24(8):1277–94.
88. Schasfoort RB. Handbook of surface plasmon resonance. London: Royal Society of Chemistry; 2017.
89. Mayer KM, Hafner JH. Localized surface plasmon resonance sensors. Chem Rev. 2011;111(6):3828–57.
90. Lyon LA, Keating CD, Fox AP, Baker BE, He L, Nicewarner SR, Mulvaney SP, Natan MJ. Raman spectroscopy. Anal Chem. 1998;70(12):341–62.
91. O'sullivan C, Guilbault G. Commercial quartz crystal microbalances-theory and applications. Biosens Bioelectron. 1999;14(8–9):663–70.
92. Wartchow CA, Podlaski F, Li S, Rowan K, Zhang X, Mark D, Huang K-S. Biosensor-based small molecule fragment screening with biolayer interferometry. J Comput Aided Mol Des. 2011;25(7):669–76.
93. Länge K, Rapp BE, Rapp M. Surface acoustic wave biosensors: a review. Anal Bioanal Chem. 2008;391:1509–19.
94. Strianese M, Staiano M, Ruggiero G, Labella T, Pellecchia C, D'Auria S. Fluorescence-based biosensors. Spectrosc Methods Anal Methods Protoc. 2012;875:193–216.
95. Zhang G-J, Ning Y. Silicon nanowire biosensor and its applications in disease diagnostics: a review. Anal Chim Acta. 2012;749:1–15.
96. Inan H, Poyraz M, Inci F, Lifson MA, Baday M, Cunningham BT, Demirci U. Photonic crystals: emerging biosensors and their promise for point-of-care applications. Chem Soc Rev. 2017;46(2):366–88.
97. Mok W, Li Y. Recent progress in nucleic acid aptamer-based biosensors and bioassays. Sensors. 2008;8(11):7050–84.
98. Omar NAS, Fen YW, Saleviter S, Daniyal WMEMM, Anas NAA, Ramdzan NSM, Roshidi MDA. Development of a graphene-based surface plasmon resonance optical sensor chip for potential biomedical application. Materials. 2019;12(12):1928.
99. Shumaker-Parry JS, Campbell CT. Quantitative methods for spatially resolved adsorption/desorption measurements in real time by surface plasmon resonance microscopy. Anal Chem. 2004;76(4):907–17.
100. Chang C-C. Recent advancements in aptamer-based surface plasmon resonance biosensing strategies. Biosensors. 2021;11(7):233.
101. Zhu R, Martínez-Roque MA, Figueroa-Miranda G, Hu Z, Acunzo A, Li H, Hu Q, Bednar J, Gensch T, Ingebrandt S, et al. Plasmon-enhanced fluorescence and electrochemical aptasensor for sars-cov-2 spike protein detection. Talanta. 2025;281: 126760.
102. Wu W, Zhu Z, Li B, Liu Z, Jia L, Zuo L, Chen L, Zhu Z, Shan G, Luo S-Z. A direct determination of afbs in vinegar by aptamer-based surface plasmon resonance biosensor. Toxicon. 2018;146:24–30.
103. Amano R, Takada K, Tanaka Y, Nakamura Y, Kawai G, Kozu T, Sakamoto T. Kinetic and thermodynamic analyses of interaction between a high-affinity rna aptamer and its target protein. Biochemistry. 2016;55(45):6221–9.
104. Duanghathaipornsuk S, Shen B, Cameron BD, Ijäs H, Linko V, Kostiainen MA, Kim D-S. Aptamer-embedded dna origami cage for detecting (glycated) hemoglobin with a surface plasmon resonance sensor. Mater Lett. 2020;275: 128141.
105. Chen Y, Nakamoto K, Niwa O, Corn RM. On-chip synthesis of rna aptamer microarrays for multiplexed protein biosensing with spr imaging measurements. Langmuir. 2012;28(22):8281–5.
106. Inoue S, Seyama M, Miura T, Horiuchi T, Iwasaki Y, Takahashi J-i, Hayashi K, Tamechika E. A reliable aptamer array prepared by repeating inkjet-spotting toward on-site measurement. Biosens Bioelectron. 2016;85:943–9.
107. Simon L, Bognár Z, Gyurcsányi RE. Finding the optimal surface density of aptamer monolayers by spr imaging detection-based aptamer microarrays. Electroanalysis. 2020;32(4):851–8.
108. Bonnet H, Coche-Gueérente L, Defrancq E, Spinelli N, Heyden A, Dejeu J. Negative spr signals during low molecular weight analyte recognition. Anal Chem. 2021;93(8):4134–40.
109. Caglayan MO. Aptamer-based ellipsometric sensor for ultrasensitive determination of aminoglycoside group antibiotics from dairy products. J Sci Food Agric. 2020;100(8):3386–93.

110. Hu J, Fu K, Bohn PW. Whole-cell pseudomonas aeruginosa localized surface plasmon resonance aptasensor. Anal Chem. 2018;90(3):2326–32.
111. Kotlarek D, Curti F, Vorobii M, Corradini R, Careri M, Knoll W, Rodriguez-Emmenegger C, Dostalek J. Surface plasmon resonance-based aptasensor for direct monitoring of thrombin in a minimally processed human blood. Sens Actuators, B Chem. 2020;320: 128380.
112. Sun D, Wu Y, Chang S-J, Chen C-J, Liu J-T. Investigation of the recognition interaction between glycated hemoglobin and its aptamer by using surface plasmon resonance. Talanta. 2021;222: 121466.
113. Wang W-W, Han X, Chu L-Q. Polyadenine-mediated immobilization of aptamers on a gold substrate for the direct detection of bacterial pathogens. Anal Sci. 2019;35(9):967–72.
114. Mihai I, Vezeanu A, Polonschii C, Albu C, Radu G-L, Vasilescu A. Label-free detection of lysozyme in wines using an aptamer based biosensor and spr detection. Sens Actuators, B Chem. 2015;206:198–204.
115. Singh V. Ultrasensitive quantum dot-coupled-surface plasmon microfluidic aptasensor array for serum insulin detection. Talanta. 2020;219: 121314.
116. Kim S, Lee S, Lee HJ. An aptamer-aptamer sandwich assay with nanorod-enhanced surface plasmon resonance for attomolar concentration of norovirus capsid protein. Sens Actuators, B Chem. 2018;273:1029–36.
117. Wang Q, Zou L, Yang X, Liu X, Nie W, Zheng Y, Cheng Q, Wang K. Direct quantification of cancerous exosomes via surface plasmon resonance with dual gold nanoparticle-assisted signal amplification. Biosens Bioelectron. 2019;135:129–36.
118. Liao G, Liu X, Yang X, Wang Q, Geng X, Zou L, Liu Y, Li S, Zheng Y, Wang K. Surface plasmon resonance assay for exosomes based on aptamer recognition and polydopamine-functionalized gold nanoparticles for signal amplification. Microchim Acta. 2020;187(4):251.
119. Kwon MJ, Lee J, Wark AW, Lee HJ. Nanoparticle-enhanced surface plasmon resonance detection of proteins at attomolar concentrations: comparing different nanoparticle shapes and sizes. Anal Chem. 2012;84(3):1702–7.
120. Baek SH, Wark AW, Lee HJ. Dual nanoparticle amplified surface plasmon resonance detection of thrombin at subattomolar concentrations. Anal Chem. 2014;86(19):9824–9.
121. Jang HR, Wark AW, Baek SH, Chung BH, Lee HJ. Ultrasensitive and ultrawide range detection of a cardiac biomarker on a surface plasmon resonance platform. Anal Chem. 2014;86(1):814–9.
122. Chen H, Hou Y, Ye Z, Wang H, Koh K, Shen Z, Shu Y. Label-free surface plasmon resonance cytosensor for breast cancer cell detection based on nano-conjugation of monodisperse magnetic nanoparticle and folic acid. Sens Actuators, B Chem. 2014;201:433–8.
123. Chen H, Qi F, Zhou H, Jia S, Gao Y, Koh K, Yin Y. Fe3o4@ au nanoparticles as a means of signal enhancement in surface plasmon resonance spectroscopy for thrombin detection. Sens Actuators, B Chem. 2015;212:505–11.
124. Vance SA, Sandros MG. Zeptomole detection of c-reactive protein in serum by a nanoparticle amplified surface plasmon resonance imaging aptasensor. Sci Rep. 2014;4(1):5129.
125. Lou Z, Wan J, Zhang X, Zhang H, Zhou X, Cheng S, Gu N. Quick and sensitive spr detection of prion disease-associated isoform (prpsc) based on its self-assembling behavior on bare gold film and specific interactions with aptamer-graphene oxide (ago). Colloids Surf B. 2017;157:31–9.
126. Arshavsky-Graham S, Urmann K, Salama R, Massad-Ivanir N, Walter J-G, Scheper T, Segal E. Aptamers vs. antibodies as capture probes in optical porous silicon biosensors. Analyst. 2020;145(14):4991–5003.
127. Kong D, Thompson IA, Maganzini N, Eisenstein M, Soh HT. Aptamer-antibody chimera sensors for sensitive, rapid, and reversible molecular detection in complex samples. ACS Sens. 2024;9:1168.
128. Choi J-H, Lee J-H, Son J, Choi J-W. Noble metal-assisted surface plasmon resonance immunosensors. Sensors. 2020;20(4):1003.
129. Sagle LB, Ruvuna LK, Ruemmele JA, Van Duyne RP. Advances in localized surface plasmon resonance spectroscopy biosensing. Nanomedicine. 2011;6(8):1447–62.
130. Kim DM, Park JS, Jung S-W, Yeom J, Yoo SM. Biosensing applications using nanostructure-based localized surface plasmon resonance sensors. Sensors. 2021;21(9):3191.
131. Prasad J. Sensing applications of biofunctionalised plasmonic gold nanoparticles. PhD thesis, Mainz, Univ., Diss., 2015, 2015.
132. Nguyen DD, Lee S, Kim I. Recent advances in metaphotonic biosensors. Biosensors. 2023;13(6):631.
133. Unser S, Bruzas I, He J, Sagle L. Localized surface plasmon resonance biosensing: current challenges and approaches. Sensors. 2015;15(7):15684–716.
134. Yoo SM, Kim D-K, Lee SY. Aptamer-functionalized localized surface plasmon resonance sensor for the multiplexed detection of different bacterial species. Talanta. 2015;132:112–7.
135. Park J-H, Byun J-Y, Shim W-B, Kim SU, Kim M-G. High-sensitivity detection of atp using a localized surface plasmon resonance (lspr) sensor and split aptamers. Biosens Bioelectron. 2015;73:26–31.
136. Xie L, Yan X, Du Y. An aptamer based wall-less lspr array chip for label-free and high throughput detection of biomolecules. Biosens Bioelectron. 2014;53:58–64.
137. Anfossi L, Di Nardo F, Cavalera S, Giovannoli C, Baggiani C. Multiplex lateral flow immunoassay: an overview of strategies towards high-throughput point-of-need testing. Biosensors. 2018;9(1):2.
138. Chakraborty D, Mukherjee A, Ethiraj K. Gold nanorod-based multiplex bioanalytical assay for the detection of cyfra 21–1 and ca-125: towards oral cancer diagnostics. Anal Methods. 2022;14(37):3614–22.
139. Park S-H, You Y. Gold nanoparticle-based colorimetric biosensing for foodborne pathogen detection. Foods. 2023;13(1):95.
140. Jazayeri M, Amani H, Pourfatollah A, Avan A, Ferns G, Pazoki-Toroudi H. Enhanced detection sensitivity of prostate-specific antigen via psa-conjugated gold nanoparticles based on localized surface plasmon resonance: Gnp-coated anti-psa/lspr as a novel approach for the identification of prostate anomalies. Cancer Gene Ther. 2016;23(10):365–9.
141. Mattarozzi M, Toma L, Bertucci A, Giannetto M, Careri M. Aptamer-based assays: strategies in the use of aptamers conjugated to magnetic micro-and nanobeads as recognition elements in food control. Anal Bioanal Chem. 2022;414:1–12.
142. Liu B, Huang R, Yu Y, Su R, Qi W, He Z. Gold nanoparticle-aptamer-based lspr sensing of ochratoxin a at a widened detection range by double calibration curve method. Front Chem. 2018;6:94.
143. Zhou C, Yu Z, Yu W, Liu H, Zhang H, Guo C. Split aptamer-based detection of adenosine triphosphate using surface enhanced raman spectroscopy and two kinds of gold nanoparticles. Microchim Acta. 2019;186:1–9.

144. Oh SY, Heo NS, Shukla S, Cho H-J, Vilian AE, Kim J, Lee SY, Han Y-K, Yoo SM, Huh YS. Development of gold nanoparticle-aptamer-based lspr sensing chips for the rapid detection of salmonella typhimurium in pork meat. Sci Rep. 2017;7(1):10130.
145. Zahra Qua, Khan QA, Luo Z. Advances in optical aptasensors for early detection and diagnosis of various cancer types. Front Oncol. 2021;11: 632165.
146. Zahra Q, Khan QA, Luo Z. Advances in optical aptasensors for early detection and diagnosis of various cancer types. Front Oncol. 2021;11: 632165.
147. Cerchia L. Aptamers: promising tools for cancer diagnosis and therapy. Basel: MDPI; 2018.
148. Hu X, Zhang D, Zeng Z, Huang L, Lin X, Hong S. Aptamer-based probes for cancer diagnostics and treatment. Life. 2022;12(11):1937.
149. Guo W, Zhang C, Ma T, Liu X, Chen Z, Li S, Deng Y. Advances in aptamer screening and aptasensors' detection of heavy metal ions. J Nanobiotechnol. 2021;19:1–19.
150. Ge S, Ma X. Electrochemical aptamer-based sensors for the detection of heavy metals. Int J Electrochem Sci. 2022;17(9): 220926.
151. Hendrickson OD, Taranova NA, Zherdev AV, Dzantiev BB, Eremin SA. Fluorescence polarization-based bioassays: new horizons. Sensors. 2020;20(24):7132.
152. Farid S, Ghosh S, Dutta M, Stroscio MA. Aptamer-based optical and electrochemical sensors: a review. Chemosensors. 2023;11(12):569.
153. Lee M, Shin S, Kim S, Park N. Recent advances in biological applications of aptamer-based fluorescent biosensors. Molecules. 2023;28(21):7327.
154. Guliy OI, Karavaeva OA, Smirnov AV, Eremin SA, Bunin VD. Optical sensors for bacterial detection. Sensors. 2023;23(23):9391.
155. Zhang Y, Tang H, Chen W, Zhang J. Nanomaterials used in fluorescence polarization based biosensors. Int J Mol Sci. 2022;23(15):8625.
156. Liu L, Zhao Q. A simple fluorescence anisotropy assay for detection of bisphenol a using fluorescently labeled aptamer. J Environ Sci. 2020;97:19–24.
157. Ma P, Duan N, Ye H, Xia Y, Ding Z, Wang Z. Selection, truncation and fluorescence polarization based aptasensor for weissella viridescens detection. Talanta. 2022;246: 123499.
158. Pehlivan ZS, Torabfam M, Kurt H, Ow-Yang C, Hildebrandt N, Yüce M. Aptamer and nanomaterial based fret biosensors: a review on recent advances (2014–2019). Microchim Acta. 2019;186:1–22.
159. Wang H-X, Zhao Y-W, Li Z, Liu B-S, Zhang D. Development and application of aptamer-based surface-enhanced raman spectroscopy sensors in quantitative analysis and biotherapy. Sensors. 2019;19(17):3806.
160. Dong S, Zhu Z, Shi Q, He K, Wu J, Feng J. Development of aptamer surface-enhanced raman spectroscopy sensor based on fe3o4@ pt and au@ ag nanoparticles for the determination of acetamiprid. Microchim Acta. 2024;191(5):289.
161. Minopoli A, Acunzo A, Della Ventura B, Velotta R. Nanostructured surfaces as plasmonic biosensors: a review. Adv Mater Interfaces. 2022;9(2):2101133.
162. Law CS, Lim SY, Abell AD, Voelcker NH, Santos A. Nanoporous anodic alumina photonic crystals for optical chemo-and biosensing: fundamentals, advances, and perspectives. Nanomaterials. 2018;8(10):788.
163. Sreekanth KV, Zeng S, Yong K-T, Yu T. Sensitivity enhanced biosensor using graphene-based one-dimensional photonic crystal. Sens Actuators, B Chem. 2013;182:424–8.
164. Sai V, Kundu T, Deshmukh C, Titus S, Kumar P, Mukherji S. Label-free fiber optic biosensor based on evanescent wave absorbance at 280 nm. Sens Actuators, B Chem. 2010;143(2):724–30.
165. Pasquardini L, Cennamo N, Arcadio F, Zeni L. A review of apta-pof-sensors: the successful coupling between aptamers and plastic optical fibers for biosensing applications. Appl Sci. 2022;12(9):4584.
166. Leitão C, Pereira SO, Marques C, Cennamo N, Zeni L, Shaimerdenova M, Ayupova T, Tosi D. Cost-effective fiber optic solutions for biosensing. Biosensors. 2022;12(8):575.
167. Igarashi A, Abe M, Kuroiwa S, Ohashi K, Yamada H. Enhancement of refractive index sensitivity using small footprint s-shaped double-spiral resonators for biosensing. Sensors. 2023;23(13):6177.
168. Meng H-M, Liu H, Kuai H, Peng R, Mo L, Zhang X-B. Aptamer-integrated dna nanostructures for biosensing, bioimaging and cancer therapy. Chem Soc Rev. 2016;45(9):2583–602.
169. Pol L, Acosta LK, Ferré-Borrull J, Marsal LF. Aptamer-based nanoporous anodic alumina interferometric biosensor for real-time thrombin detection. Sensors. 2019;19(20):4543.
170. Peltomaa R, Glahn-Martínez B, Benito-Peña E, Moreno-Bondi MC. Optical biosensors for label-free detection of small molecules. Sensors. 2018;18(12):4126.
171. Herrera-Domínguez M, Morales-Luna G, Mahlknecht J, Cheng Q, Aguilar-Hernández I, Ornelas-Soto N. Optical biosensors and their applications for the detection of water pollutants. Biosensors. 2023;13(3):370.
172. Wang X-H, Wang S. Sensors and biosensors for the determination of small molecule biological toxins. Sensors. 2008;8(9):6045–54.
173. Park J-H, Cho Y-W, Kim T-H. Recent advances in surface plasmon resonance sensors for sensitive optical detection of pathogens. Biosensors. 2022;12(3):180.
174. Nabok A, Al-Rubaye A, Al-Jawdah A, Tsargorodska A, Marty J-L, Catanante G, Szekacs A, Takacs E. Novel optical biosensing technologies for detection of mycotoxins. Opt Laser Technol. 2019;109:212–21.
175. Jorn C, Lai EP. Polypyrrole film on miniaturized surface plasmon resonance sensor for ochratoxin a detection. Synth Met. 2004;143(3):253–8.
176. Taylor AD, Ladd J, Etheridge S, Deeds J, Hall S, Jiang S. Quantitative detection of tetrodotoxin (ttx) by a surface plasmon resonance (spr) sensor. Sens Actuators, B Chem. 2008;130(1):120–8.
177. Pisal DS, Kosloski MP, Balu-Iyer SV. Delivery of therapeutic proteins. J Pharm Sci. 2010;99(6):2557–75.
178. Leung A, Shankar P, Mutharasan R. Real-time monitoring of bovine serum albumin at femtogram/ml levels on antibody-immobilized tapered fibers. Sens Actuators, B Chem. 2007;123(2):888–95.
179. Li Q, Wang Q, Yang X, Wang K, Zhang H, Nie W. High sensitivity surface plasmon resonance biosensor for detection of microrna and small molecule based on graphene oxide-gold nanoparticles composites. Talanta. 2017;174:521–6.
180. Li J, Lei P, Ding S, Zhang Y, Yang J, Cheng Q, Yan Y. An enzyme-free surface plasmon resonance biosensor for real-time detecting microrna based on allosteric effect of mismatched catalytic hairpin assembly. Biosens Bioelectron. 2016;77:435–41.

181. Valenzuela-Amaro HM, Aguayo-Acosta A, Meléndez-Sánchez ER, Rosa O, Vázquez-Ortega PG, Oyervides-Muñoz MA, Sosa-Hernández JE, Parra-Saldívar R. Emerging applications of nanobiosensors in pathogen detection in water and food. Biosensors. 2023;13(10):922.
182. Bong J-H, Kim T-H, Jung J, Lee SJ, Sung JS, Lee CK, Kang M-J, Kim HO, Pyun J-C. Pig sera-derived anti-sars-cov-2 antibodies in surface plasmon resonance biosensors. BioChip J. 2020;14:358–68.
183. Reaño RL, Escobar EC. A review of antibody, aptamer, and nanomaterials synergistic systems for an amplified electrochemical signal. Front Bioeng Biotechnol. 2024;12:1361469.
184. Yadav SK, Verma D, Yadav U, Kalkal A, Priyadarshini N, Kumar A, Mahato K. Point-of-care devices for viral detection: Covid-19 pandemic and beyond. Micromachines. 2023;14(9):1744.
185. Luka G, Ahmadi A, Najjaran H, Alocilja E, DeRosa M, Wolthers K, Malki A, Aziz H, Althani A, Hoorfar M. Microfluidics integrated biosensors: a leading technology towards lab-on-a-chip and sensing applications. Sensors. 2015;15(12):30011–31.
186. Thwala LN, Ndlovu SC, Mpofu KT, Lugongolo MY, Mthunzi-Kufa P. Nanotechnology-based diagnostics for diseases prevalent in developing countries: current advances in point-of-care tests. Nanomaterials. 2023;13(7):1247.
187. Sekhwama M, Mpofu K, Sivarasu S, Mthunzi-Kufa P. Applications of microfluidics in biosensing. Discov Appl Sci. 2024;6(6):303.
188. Weng C-H, Huang C-J, Lee G-B. Screening of aptamers on microfluidic systems for clinical applications. Sensors. 2012;12(7):9514–29.
189. Ghosh Dastider S, Barizuddin S, Yuksek NS, Dweik M, Almasri MF, et al. Efficient and rapid detection of salmonella using microfluidic impedance based sensing. J Sens. 2015. https://doi.org/10.1155/2015/293461.
190. Mi F, Hu C, Wang Y, Wang L, Peng F, Geng P, Guan M. Recent advancements in microfluidic chip biosensor detection of foodborne pathogenic bacteria: a review. Anal Bioanal Chem. 2022;414(9):2883–902.
191. He P, Oncescu V, Lee S, Choi I, Erickson D. Label-free electrochemical monitoring of vasopressin in aptamer-based microfluidic biosensors. Anal Chim Acta. 2013;759:74–80.
192. Nasseri B, Soleimani N, Rabiee N, Kalbasi A, Karimi M, Hamblin MR. Point-of-care microfluidic devices for pathogen detection. Biosens Bioelectron. 2018;117:112–28.
193. Granata F, Coluccio ML, Minopoli A, Cuzzola P, Costa R, Malara N, Iodice M, Coppola G, Gentile F. Optimization of microfluidic functionalization of a plasmonic-based device for selective capture of anti-folic acid in solution. Biosens Bioelectron X. 2022;12: 100226.
194. Li N, Jiang Y, Lv T, Li G, Yang F. Immunofluorescence analysis of breast cancer biomarkers using antibody-conjugated microbeads embedded in a microfluidic-based liquid biopsy chip. Biosens Bioelectron. 2022;216: 114598.
195. Liu Y, Li J, Xiao S, Liu Y, Bai M, Gong L, Zhao J, Chen D. Revolutionizing precision medicine: exploring wearable sensors for therapeutic drug monitoring and personalized therapy. Biosensors. 2023;13(7):726.
196. Yogev D, Goldberg T, Arami A, Tejman-Yarden S, Winkler TE, Maoz BM. Current state of the art and future directions for implantable sensors in medical technology: clinical needs and engineering challenges. APL Bioeng. 2023;7(3): 031506.
197. Yoshida W, Mochizuki E, Takase M, Hasegawa H, Morita Y, Yamazaki H, Sode K, Ikebukuro K. Selection of dna aptamers against insulin and construction of an aptameric enzyme subunit for insulin sensing. Biosens Bioelectron. 2009;24(5):1116–20.
198. Wu N, Zandieh M, Yang T, Liu J. Cytosine-rich dna binding insulin stronger than guanine-rich aptamers: effect of aggregation of insulin for its detection. Anal Chem. 2023;95(23):8948–55.
199. Wu Y, Midinov B, White RJ. Electrochemical aptamer-based sensor for real-time monitoring of insulin. ACS sens. 2019;4(2):498–503.
200. Chien J-C, Mage PL, Soh HT, Arbabian A. An aptamer-based electrochemical-sensing implant for continuous therapeutic-drug monitoring in vivo. In: 2019 Symposium on VLSI Circuits, IEEE. 2019;312–313.
201. Land KJ, Boeras DI, Chen X-S, Ramsay AR, Peeling RW. Reassured diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. Nat Microbiol. 2019;4(1):46–54.
202. Wang C-H, Wu J-J, Lee G-B. Screening of highly-specific aptamers and their applications in paper-based microfluidic chips for rapid diagnosis of multiple bacteria. Sens Actuators, B Chem. 2019;284:395–402.
203. Sun Y, Lin Y, Sun W, Han R, Luo C, Wang X, Wei Q. A highly selective and sensitive detection of insulin with chemiluminescence biosensor based on aptamer and oligonucleotide-aunps functionalized nanosilica@ graphene oxide aerogel. Anal Chim Acta. 2019;1089:152–64.
204. Xu W, Wang D, Li D, Liu CC. Recent developments of electrochemical and optical biosensors for antibody detection. Int J Mol Sci. 2019;21(1):134.
205. Song M, Lin X, Peng Z, Xu S, Jin L, Zheng X, Luo H. Materials and methods of biosensor interfaces with stability. Front Mater. 2021;7: 583739.
206. Wark A, Lee H, Corn R, Schasfoort R, Tudos A. Handbook of surface plasmon resonance. London: The Royal Society of Chemistry; 2008. p. 246–74.
207. Le Basle Y, Chennell P, Tokhadze N, Astier A, Sautou V. Physicochemical stability of monoclonal antibodies: a review. J Pharm Sci. 2020;109(1):169–90.
208. Kumar S, Wang Z, Zhang W, Liu X, Li M, Li G, Zhang B, Singh R. Optically active nanomaterials and its biosensing applications-a review. Biosensors. 2023;13(1):85.
209. Gómez-Arribas LN, Benito-Peña E, Hurtado-Sanchez MdC, Moreno-Bondi MC. Biosensing based on nanoparticles for food allergens detection. Sensors. 2018;18(4):1087.
210. Beeram R, Vepa KR, Soma VR. Recent trends in sers-based plasmonic sensors for disease diagnostics, biomolecules detection, and machine learning techniques. Biosensors. 2023;13(3):328.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.