Chapter

Application of Plasmonic Nanostructures in Molecular Diagnostics and Biosensor Technology: Challenges and Current Developments

Sanele Nyembe, Andile Mkhohlakali, Bambesiwe May and Nikiwe Mhlanga

Abstract

The recent global pandemic caused by Covid-19 enforced the urgent need for accessible, reliable, and accurate point-of-care rapid diagnostics based on plasmonic nanostructures. This is because fast and reliable testing was the key driver in curbing the spread of Covid-19. The traditional methods of diagnostics and biosensors often require expensive infrastructure and highly qualified and trained personnel, which limits their accessibility. These limitations perpetuated the impact of Covid-19 in most countries because of the lack of easily accessible point-of-care rapid diagnostic kits. This review revealed that portable and reliable point-of-care diagnostic kits are very crucial in reaching large populations, especially in underdeveloped and developing countries. This gives perspective to novel point-of-care applications. Furthermore, water quality is a very crucial part of food safety, especially in developing countries faced with water contamination. In this chapter, we explored the various challenges and recent developments in the use of plasmonic nanostructures for application in molecular diagnostics and biosensing for the detection of infectious diseases and common environmental pathogens.

Keywords: plasmon, molecular diagnostic, surface plasmon resonance (SPR), nanostructures, infectious diseases, water pathogens, machine learning, SERS

1. Introduction

Traditional gold-standard diagnostic techniques combined with advances in nucleic acid-based assays, enzyme-linked immunoassays, and rapid diagnostic assays are widely used for the detection of diseases. Despite the advances presented by these techniques several hurdles such as false positives/negatives, expensive infrastructure or equipment, non-specificity, complicated sample preparation, and assay result analysis limit their use. This is evidenced by the continued world health organization cases reported from low-resource regions. The need for affordable, specific, simple, user-friendly, rapid, and sensitive, diagnostics remains.

Plasmonic-based diagnostics or biosensors offer an attractive solution in the detection and management of diseases. They can achieve enhanced sensitivity, rapidity, real-time and label-free detection of pathogenic biomarkers [1, 2]. The plasmonic phenomenon yields various techniques: Surface Plasmon Resonance (SPR), Localized Surface Plasmon Resonance (LSPR), colorimetric Plasmonic assays, Surface-Enhanced Raman spectroscopy (SERS) and its variants. Benefiting the diagnostic fraternity, Plasmonic-based assays are merited with a multiplexing potential and smartphone integration [1]. The Plasmonic based sensing platform extends to environmental sensing. Water contamination due to pathogens and biological molecules such as Covid-19 benefits from Plasmonic sensors. In addition to detection, the plasmonic sensors can quantify the pathogens in the drinking waters to inform water treatment measures to be taken.

SPR biosensing is based on the excitation of the free electrons by a polarized light on a metal film which onsets the electrons' collective oscillation [1–3]. A plasmonic surface is immobilized with biomarker receptors, which bind the analyte and induce a change in the local refractive index. The change is perceived through changes in the incident light used for the excitation of the free electrons to the SPR state [1]. This principle has resulted in paradigms for different diseases: malaria [4–6], tuberculosis [7–9], HIV [10, 11], and Covid-19 [12].

The LSPR is based on the confined oscillation of electrons at the metallic surface and the localized SPR distinguishes LSPR from the propagating SPR biosensor. Interaction of the receptor with an analyte in LSPR biosensing induces changes that prompt a wavelength shift in the excitation spectrum. The LSPR-based sensors are excellent for both the detection and quantification of biomolecules/diseases [1, 3]. The potential for LSPR biosensing has been tested on Covid-19 [13], glucose [14], and cancer cells [15].

Colorimetric Plasmonic assays are driven by LSPR of metallic nanostructures such as gold (Au) and silver (Ag) that yield enhanced magnetic fields in the visible/NIR range. This phenomenon yields color changes observed by the naked eye. The color changes merit colorimetric plasmonic assays for point-of-care testing [1, 16].

SERS principle uses the plasmonic effect of the metallic substrates to enhance weak traditional Raman signals. Raman spectroscopy is a fingerprinting tool that is used to study characteristic peaks of molecules. However, its sensitivity is compromised for some molecules especially biomolecules limiting its use in diagnostics. SERS alleviates the low signal challenge by amplifying the weaker signals and availing the technique for biosensing. It is used as either label-free for Raman active analytes or labeled for non-Raman active molecules. Zhou et al. developed an AgNPs based sensor for the detection of bacteria from drinking water. The SERS substrate, AgNPs coats on the cell wall of the bacteria and enhances the Raman signal of the analyte by 30-folds compared to a non-coating AgNPs colloids. The chapter examines the potential for plasmonic-based assays in the detection of diseases and common water pathogens. It compares literature and prototypes in the field and future expectations.

2. Plasmonic nanostructures in biosensing

Biosensors are significant in a variety of scientific domains, including clinical diagnostics, medical diagnostics, illicit drug detection, food quality and safety, and

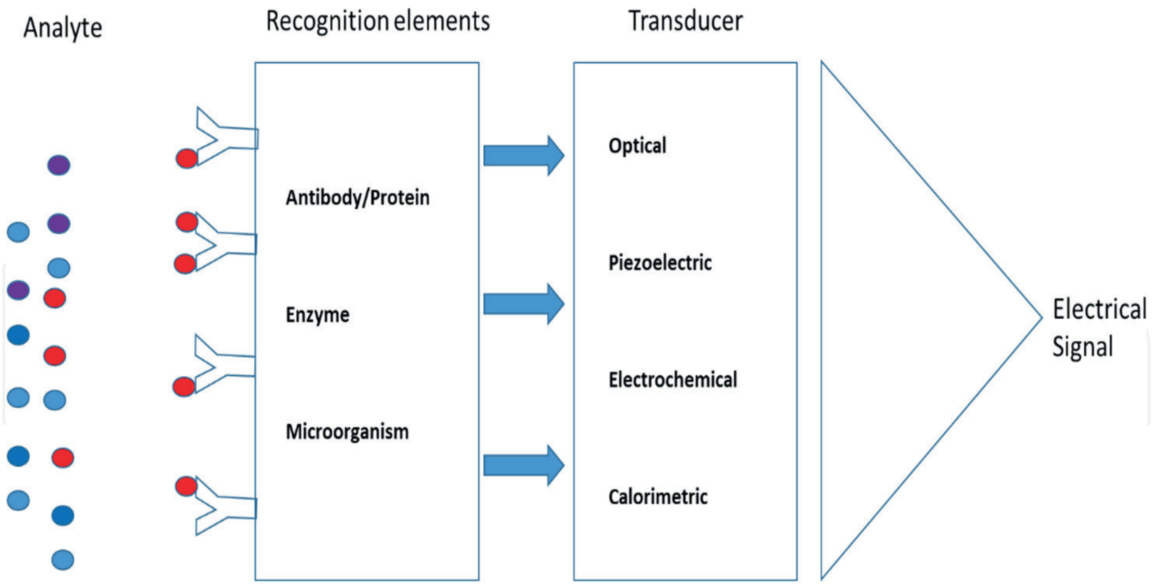

Figure 1.
General schematic for biosensor as adopted from literature [19].

environmental evaluation [17]. Biosensor is an analytical device, which consists of two basic components: the recognition unit employed to capture the specific target and the transducer that converts the biomolecule interaction into an electrical, chemical, or optical signal. The types of biosensor depend on the types of output signal measured and quantified in real-time [18]. As depicted in **Figure 1**, the identification of stimulus is released after the interaction of the sensing surface with the analyte and converts it into a detectable signal.

2.1 Types of biosensors

Biosensors can be classified according to the output as shown in **Figure 2**. In addition, all these types share a common working principle. Furthermore, electrochemical biosensors are sub-classified into impedimetric, voltammetric, potentiometric, and amperometric. Among these, bio-sensing types, electrochemical sensor is considered as conventional sensor and has been under an extensive search for years. It has attracted interest in several fields such as health, food, and agriculture [3]. However, plasmonic biosensing possesses many advantages over traditional (electrochemical) sensors due to their (i) label-free detection, (ii) real-time, (iii) short response time, and (iv) simple sample preparation.

2.2 Plasmonic bio-sensing mechanism and sensing principle

2.2.1 Surface plasmon resonance (SPR)

Surface plasmon resonance (SPR) biosensor (**Figure 3**) is one of the important tools for examining the kinetics of biomolecular interaction with the surface and they offer a unique real-time and label-free measurements, non-invasive nature with high detection sensitivity [21]. SPR is a frequently used optical technique for tracking changes in a sensor layer's refractive index (RI) after interaction with a target molecule [3]. SPR has been widely used in various detection of biological and chemical analytes, for environmental and agricultural monitoring [22]. It is a metal-based film

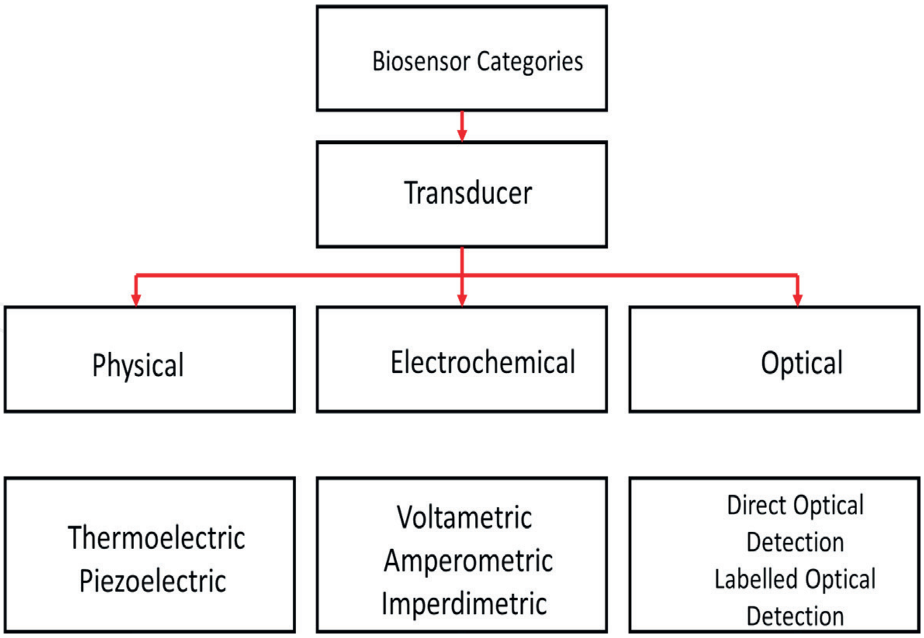

Figure 2.
Types of biosensor based on their transducer identity [18].

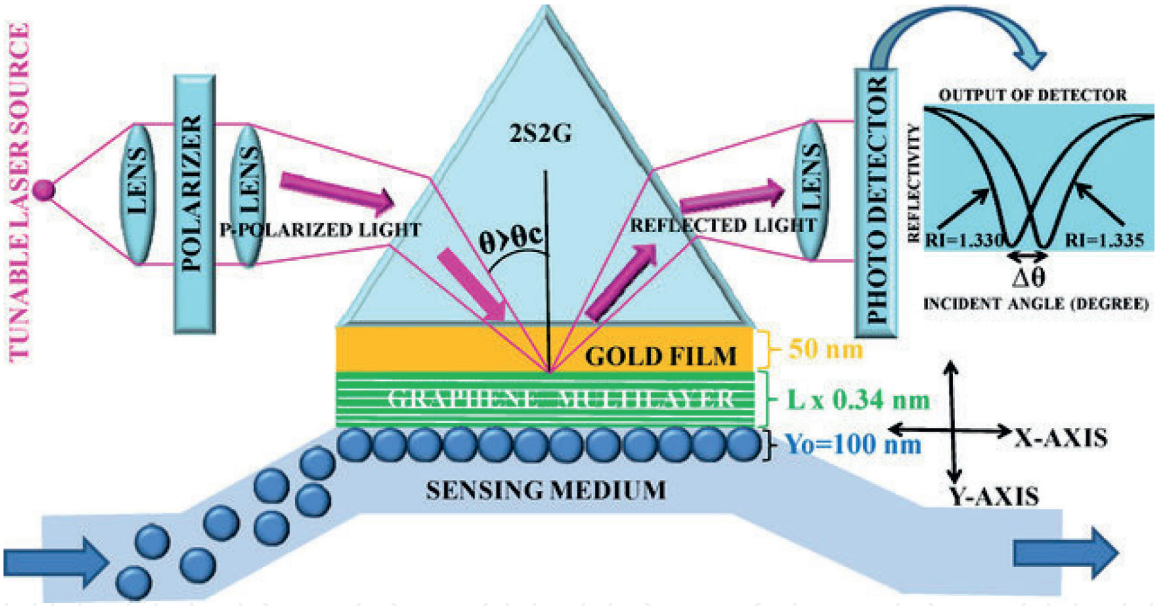

Figure 3.
Schematic of SPR biosensor experimental set up (a) [20], adopted from literature [10] copyrights, SPR (a) and LSPR (b) sensing mechanism (c).

sensor, made of gold (Au), which is used to characterize biomolecular interactions [23]. SPR systems are based on an optical phenomena pioneered by Wood in the 1980s, which is a gold standard method. The most successful plasmonic up to date, based on optical label-free sensing technology. Wang et al. used hepatitis B surface (HBs) antigen as the target molecule and gold nanorods (AuNRs) to realize LSPR for an HBV sensor [3]. Ever since, there has been ongoing research on developments of label-free, real-time, and ultra-sensitive SPR for the sensing of small and large biomolecules which is based on monitoring of refractive index (RI) changes in the surrounding environment (surface chip sensor) caused by biomolecular interaction around sensing area [24]. These technologies have been widely used in drug screening and in other biomedical disciplines. Bai and co-workers presented an SPR-based biosensor for the detection of the avian influenza virus (AIV) H5N1. Employing a chosen aptamer as the recognition element [3].

Figure 3(a) and **(b)** depicts the SPR sensing mechanism, it can be observed as electromagnetic surface waves that are solution of Max equation. SPR occurs at the interface of the bulk materials with positive dielectric constant and of a negative dielectric constant of the metals (precious metals: Au, Ag) [25]. The electron clouds propagate horizontal (x-y) plane to hundreds of micrometers along the metal-dielectric interface and their lateral extensions and eventually decay exponentially away into both sides of the interface in z-axis [3].

In contrast to SPR, LSPR sensing mechanism (**Figure 3(c)**), the electromagnetic waves are confined and no-propagating surface plasmon at the surface of an isolated metallic nanostructure. As the curve metallic surface of nanoparticle, the interaction between electromagnetic waves applies the restoring force to oscillating electron cloud and amplifies the electromagnetic resonance (EM) field of the metal interface due to resonance. In addition, the light-matter interaction is where LSPR originates [26]. When it comes to plasmonic nanostructures, surface plasmons are restricted to a narrow area near the nanostructures and sensitive to RI changes.

The EM field enhancement can scrutinized and quantified on the metallic surface may be explained using Mie Theory (Eq. (1)), which is frequently used for electromagnetic simulations.

Mie theory;

$$\partial = 4\pi r^3 \frac{\in - \in m}{\in + 2 \in m} \tag{1}$$

where R and ∂ is a permeability and the radius of the metal nanoparticles. The EM field is sensitive to the changes of RI of the dielectric layer, which has a potential to be used as sensing layer for SPR based sensor realization. Kretschmann and Reather pioneered the creation of SPR-based sensors in 1968 by introducing the traditional prism-based structure, while Liedberg et al. reported the first experimental demonstration of exploiting the phenomenon for sensing. Plenty of companies to manufacture point-of-cars (POCs) facilities have utilized these technologies (SPR) sensor mechanism.

2.2.2 Localized surface plasmon resonance biosensors (LSPR)

The bioanalytical community has been interested in localized surface plasmon resonance (LSPR) phenomenon. LSPR has many of the same benefits as traditional propagating SPR, but with a few key differences. In comparison to SPR, LSPR has the following benefits: a high aspect ratio that allows for a larger interaction surface area for immobilizing the sensing elements; a miniature probe to produce compact devices; and broad applicability and compatibility with several phenomena, including fluorescence, Raman, and IR spectroscopy. In LSPR, the interaction of the electromagnetic waves and sub-wave metal NPs gives a rise to non-propagating oscillations of the collected electron conducted cloud against metal positive core, this phenomenon is localized surface Plasmon [27]. LSPR operates with the same merits as traditional propagating SPR, however with additional crucial advantages. One of the examples, they are more suitable to microchip integration, faster response time and have much better spatial resolution [28]. Moreover, LSPR has high aspect ratio, thus allowing more interaction surface area for immobilizing the sensing elements to obtain compact devices and wide stability, compatibility, and applicability towards phenomenon such fluorescence, and Raman and IR spectroscopy to name the few. Researchers have devoted efforts in contribution to the development of noble metal-based LSPR on a planer surface [28]. However, so far, the development of LSPR is restricted at the laboratory scale due to the fundamental limits of noble metals such as their high price and their high production cost [26].

2.2.3 Plasmonic nanostructures in biosensing

Nanostructures offer a wide range of potential uses in biosensors because of their distinctive size-tuneable and shape-dependent physicochemical features. The field of optical biosensors enters a new age with the incorporation of nanostructures and useful biological molecules (such as antibodies, nucleic acids, and peptides) [22]. Loideau et al. have reported the Ag and Ag@Au NPs based LSPR for application in naked-eye biosensing, utilizing color change from cyan to green [28]. In the last two decades, Plasmon resonance in gold nanoparticles (Au NPs) has been the subject of intense research efforts. However, the inflated cost for precious metal such as Ag and Au has been a great concern.

Recently, due to the inflated cost, production cost of noble metals, researchers have paid a considerable attention to the development of non-noble metal and semiconductor materials. As potential replacements for plasmonic noble metals, low-cost and resource-rich non-noble metal plasmonic materials have drawn significant interest [29]. The commonly used non-noble plasmonic material reports are copper-based, Aluminum, semiconductor, and graphene-based LSPR. Non-noble metal like bismuth (Bi) have similar plasmonic properties as precious metal. Chen et al. have reported the synthesis of non-noble (Bi/$BiVO_4$) as photoanode sensing materials for application in detection of H_2O_2 [30]. Zhu et al. reported sponge-like surface-enhanced scattering (SERS) substrate in which reduced graphene oxide used to wrap the Ag nanotube for detection of dithiocarbomates pesticide [31]. Among the support surface for LSPR, glass substrates have been the most popular and been attracted considerable attention for LSPR sensor platform. The LSRP sensing mechanism has been recently been utilized in sensing the eloba virus by Tsang et al. and the nanoparticle have been able to sense the virus at lowest LOD level. While and Li et al. reported the detection of SARS-COV-2 (COVID-19) [29].

2.2.4 Bottom-up fabrication methods developments of plasmonic biosensors

Among the fabrication approaches for plasmon biosensors, bottom-up approach has attracted prodigious interest due to control over the structure, shape, and size as compared to top-down approach. Top-down approach uses lithographic etching, which is associated with undesirable structures. The unique and extremely sensitive nanostructures of SPR and LSPR properties, together with generality of fabrication method used obviate the undesirable optical and structural effect associated lithographical prepared nanostructures for sensing applications. The size and shape of the nanostructures are of great interest, due to their huge influences in fine-tuning the sensitivity due to an enhanced interaction surface area and electric properties compared to the bulk material counterparts. A novel way to get around the constraints of a traditional SPR biosensor's detection limit, sensitivity, selectivity, and throughput provided by recent developments in nanofabrication techniques and nanoparticle syntheses.

Before every step in plasmonic nanostructures developments is the fabrication approach. The fabrication method influences the physical and chemical identity/nature of plasmonic materials, which is the size, and structural morphology to name few. These properties turn to determine the plasmonic biosensor activity. Nanotechnology and nanostructures have shown a great interest in contributing towards the nanoplasmonic materials, which entails biosensing and biological application, through manipulating the sensitivity [32]. Nanostructures as the driving force of nanotechnology, hold the futuristic technological developments of portable devices, and drive the next technology generation such as the fourth industrial revolution (4IR) and machine learning [33, 34].

The recent progress in the fabrication of advanced smart nanostructures find a widely application in the environmental and biological disciplines. In addition, the effort to fabricate nanoplasmonic biosensors based on LSPR mostly noble metal (Au or Ag), to reduce cost, expensive equipment, and these materials exhibited unmatched characteristic features that can be utilized [35]. In this regard, the optical characteristics of metallic nanostructures such as Au and Ag nanoparticles (NPs) have been developed and utilized to create simple, fast-responding, and low-cost nanodiagnostic and nanotherapeutic smart systems due to their chemical stability and biocompatibility [36]. In fact, due to their intense interactions with light, AuNPs and AgNPs are specifically studied for their optical features [37].

Masterson et al. reported the bottom-up synthesis of AuNPs, AuNRs [38]. There are many methods used to fabricate plasmon nanostructures with various morphologies, that is, nanoplates, nanorods, nanosphere, nanoarrays, etc. [39] as shown in **Table 1**. Kim and co-workers reported the nanoarrays using electron beam lithography, for detection of avian DNA-Influenza utilizing the SPR [45]. In 2018, Liu et al. reported the Au nanoplates using the hydrothermal synthesis for the sensing of, [46].

2.2.5 The limitation of plasmonic biosensors

The inability to consistently detect minor changes in refractive index brought on by substances in low concentration at the sensor surface is one of the primary issues preventing the further development of SPR applications. The expense of noble metals used in plasmonic biosensors. In addition, there are still many obstacles to overcome, both now and in the future, despite the recent boom in the development of nanomaterial-based plastic sensors for POC facilities applications. Among the technology bottleneck, researcher mostly discuss the plasmonic biosensors that are urgent which limits the development of biosensors. The first one is the Covid-19 global pandemic,

Fabrication method	Materials	Application	Ref
Template method	Au nano slit		[40]
Chemical reduction	Ag nanoparticles		[41]
Seed-mediated growth	Au nanorod	Detection of tuberculosis	[42]
Electrodeposition	Au, Ag, Cu	Antigen-antibody detection	[43]
Hydrothermal/solvothermal	Au nanoplates	SERS enhancement	[44]

Table 1.
Summarized list of methods for the synthesis of various nanostructures morphology and their applications.

which requires rapid, POC diagnostic facility to urgent identify contraction of the (SARS-COv-2) virus. Another challenge I to quickly develop the accurate, reliable plasmonic biosensor that is flexible in realization of 4IR and machine-learning tool that can easily use to predict the sensing properties of the nanoparticles [44].

3. Biosensing for environmental monitoring

The increased industrial and agricultural activities have increased the levels of chemical and biological substances being release into the environment. Thus, environmental monitoring is mandatory. This drives the need for real-life detection with rapid measurements that allows environmental monitoring in various real-life situations. Plasmonic biosensors have shown the potential to detect pollutants directly and reliably in the environment. The most common analytes detected by biosensors for environmental monitoring include heavy metals in water, pesticides, and potentially toxic and dangerous chemicals such as explosives [19, 23, 47–49]. Conventional sensing substrates have been improved with plasmonic materials for enhanced performance. The design of specific plasmonic structures made it possible for easy binding of analytes, bringing the pollutants close to the surface of the plasmonic sites [47].

3.1 Heavy metals

Heavy metals such as Cu, Hg, Pb, and Cd are among the harmful inorganic pollutants released into the environment from industrial and agricultural activities [50–52]. They do not decompose naturally and thus become persistent in water streams and agricultural land. Since their presence is regulated, their detection is mandatory to prevent diseases, protect the environment and strategize viable treatment plans to meet regulation requirements [53].

One of the most common plasmonic biosensors are colorimetric sensors. They offer convenient, rapid in field pollutant response that can be observed with the naked eye. This type of sensing is possible because the local surface Plasmon resonance peaks of the biosensors fall within the visible spectrum and the aggregation that occurs in the presence of the pollutant/analytes cause changes in color [47]. For instance, detection of Hg^{2+} ions were demonstrated using mercaptopropionic acid (MPA) capped Au NPs, where Hg ions complexed with carboxylic acid groups of MPA revealing a color change from red to colorless. The selectivity of Hg^{2+} ions among other metals was improved in the presence of 2.6-pyridinedicarboxylic acid (PDCA) due to increased complexation coefficient. As a result, a quantitative detection range of 250–500 nM with a limit of detection of 100 nM was established [54].

In another development, a rapid color change from blue to red was observed in the detection of Pb^{2+}ions with DNA zyme assembly of Au NPs (**Figure 4**) [55]. The DNA zyme assembly forms a hybrid with Au NPs, which resulted in aggregation. Furthermore, the presence of lead catalyzes the hydrolytic cleavage, which dissembles the hybrid into dispersed Au NPs bringing the color, back to red (**Figure 4**) [55].

3.2 Pesticide and explosives

The release of organic pollutants such as pesticides (used in agriculture) and polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, phenol, dioxins (by-products of combustion, incineration, and chemical manufacturing processes)

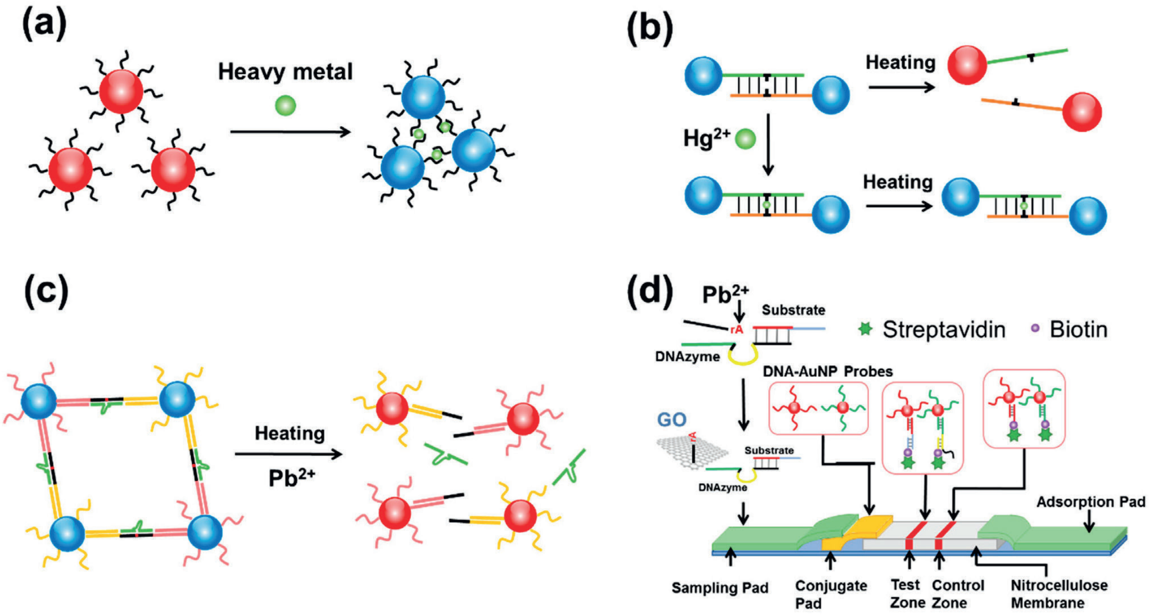

Figure 4.
DNA zyme-directed assembly formation and cleavage of Au NPs during Pb2+ ion colorimetric sensing. Reprinted with permission from Reference [55].

into the environment presents a concern for environmental protection. For example, pesticides and PAHs can accumulate in soil and water and they pose endocrine-disrupting activity, which can be a threat to human health and local ecosystems [56, 57]. Many SPR-based immunosensors have shown potential in the detection of these environmental pollutants such as atrazine, Dichloro-Diphenyl Trichloroethane (DDT), 2,3,7,8-tetrachlorodibenzo-p-dioxin, carbaryl, 2,4-D, benzo[a]pyrene (BaP), biphenyl derivatives, and trinitrotoluene (TNT) [22, 58, 59]. Recently, signal amplification for the detection of TNT was demonstrated using LSPR-based AuNPs. TNT detection occurred through the formation of a Meisenheimer complex with

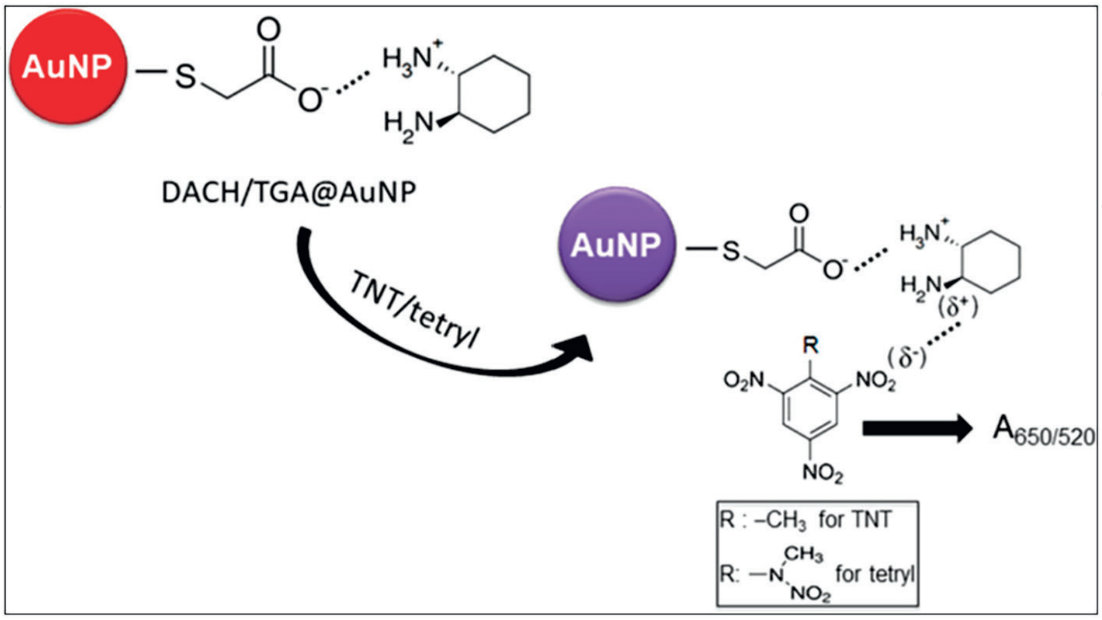

Figure 5.
The formation of Meisenheimer complex between L-cysteine capped Au NPs and TNT. Reprinted with permission from Reference [60].

L-Cysteine capped AuNPs (**Figure 5**). The electrostatic attraction between the TNT and L-cysteine capped Au NPs resulted in aggregation of the NPs. The material could detect TNT in shampoo solution demonstrating good selectivity [61]. SERS substrates based on AuNRs were applied for the detection of low levels of three dithiocarbamate fungicides. Their interaction between the pesticides and the Au-NRs resulted in the formation of Au-S covalent bonds on the surface between the pesticides and the Au-NRs. Detection limits of 34, 26, and 13 nM were discovered for thiram, firbam, zeram, respectively [60].

4. Plasmonic nanostructures in diagnostics

4.1 Molecular diagnostics assays

Historically, molecular diagnostics assays polymerase chain reaction (PCR) have played a key role in society in curbing the spread and effects of various infectious diseases through early detection [36, 62]. Even though, this technology provides fast and reliable results and do not require any post processing, its limitations are still the expensive machinery, lengthy assay times and sophisticated operational processes that often require a trained personnel [63, 64]. The fast development of nanotechnology and their use in biotechnology has shone a new light towards the use of molecular diagnostics. Specifically, the use of plasmonic nanoparticles has had a significant impact on the clinical and life science [65]. Plasmonic optical properties make them ideal for use in molecular diagnostics because they improve sensitivity, selectivity, efficiency in drug delivery and specificity [66, 67]. K. Jiang et al. reported the use plasmonic magnetic nanoparticles covered with silica core shell for the detection of DNA ranging from 0.5 ng μL^{-1} to 3 fg μL^{-1} within 20 minutes using cPCR [62, 67]. This study shows the importance of using plasmonic nanoparticles for the detection of diseases in real time that is acquit of traditional molecular diagnosis limitations such as lengthy assay times. In this study, the plasmonic magnetic nanoparticles were used for their dual function of thermal cycling and magnetic separation and detectable color change [62].

4.2 Surface-enhanced Raman scattering immunoassays

SERS-based immunoassays are a promising tool and integral for the identification of biological threats through early detection of biomarkers, which is crucial for disease control [68]. The SERS technology the plasmonic nanoparticles are functionalized with Raman reporters, which are attached to protein binding membranes. The binding membrane facilitates the detection of diseases and shows high sensitivity [69]. Gold, silver, copper, and platinum nanoparticles have been used to improve sensitivity and enhancement factor of the SERS substrate [70]. The schematic illustration of a typical SERS immunoassay is shown in **Figure 6**.

However, in recent years the SERS technology has been moving away from the use of pristine spherical nanoparticles and moving towards the different morphologies and composites. The reason for the observed shifts is due to the realization that plasmonic using pristine spherical nanoparticles does not realize the full potential of SERS in point of care tests. S. Nyembe et al. performed a comparison study of gold nanowires (diameter of 10 nm) with various gold nanoparticles (14, 30 and 40 nm) and the results showed that gold nanowires had a better enhancement factor than

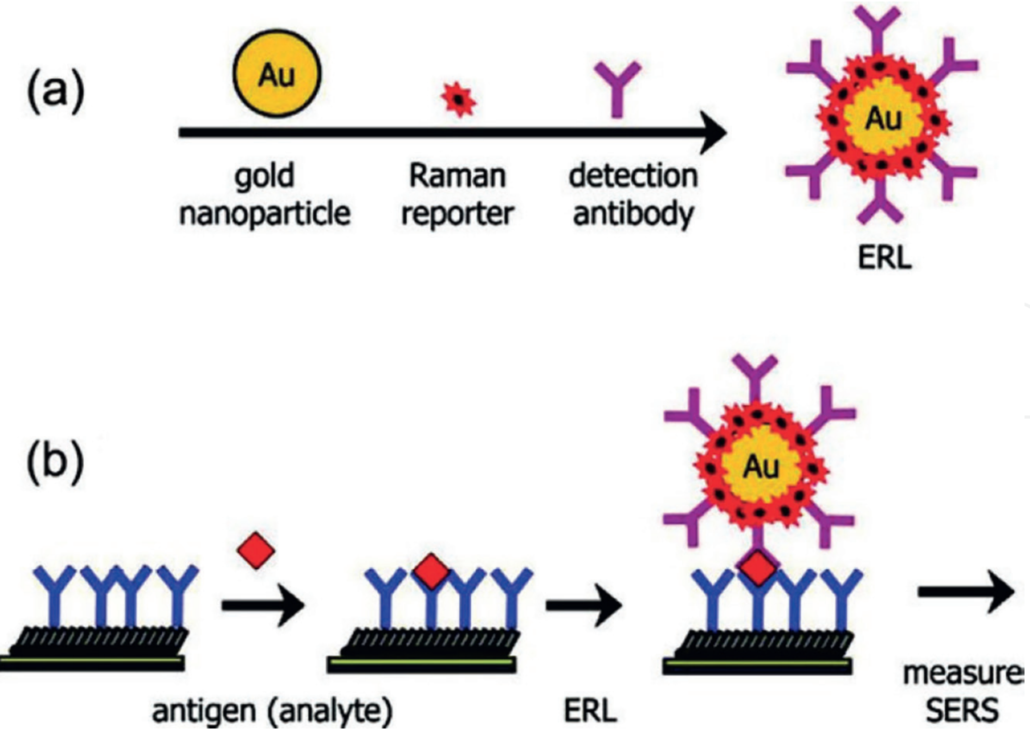

Figure 6.
Schematic illustration of a typical SERS sandwich immunoassay for biomarker detection [71].

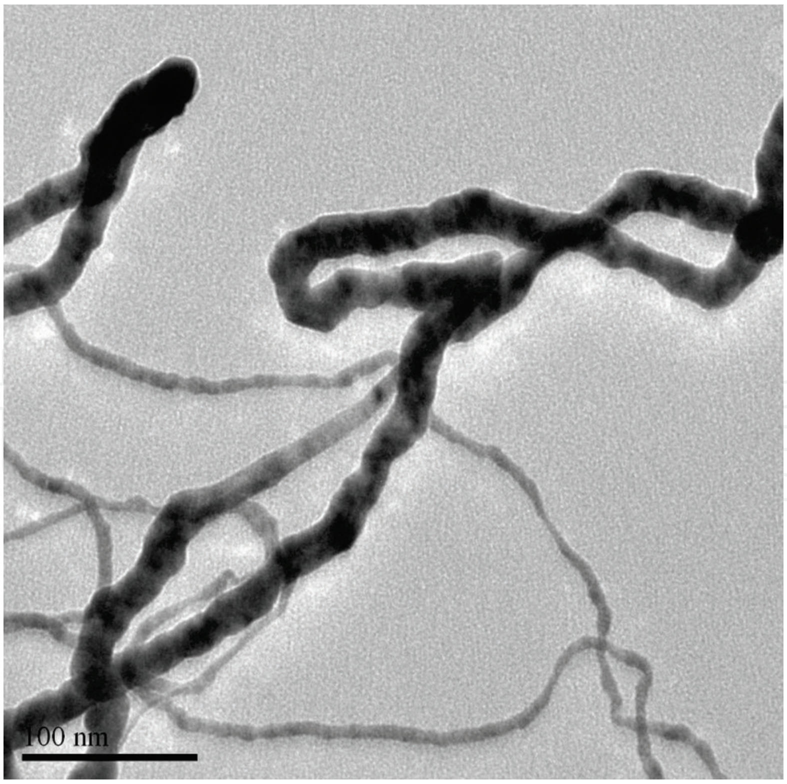

Figure 7.
TEM image of gold nanowires [72].

the spherical gold nanoparticles [72]. The higher enhancement factor was due to better adsorption capacity due to higher surface area and from entrapment caused by interstices formed by their network as shown in **Figure 7** [72].

5. Prospects of molecular diagnostics and biosensing using plasmonic nanostructures

5.1 Gold standard methods

Covid-19 is an acute respiratory disease that has infected over 500 million people worldwide and has taken lives of over 6 million people (as of November 2021). During the pandemic, governments offered tests sights in various locations to test as many people as possible using traditional testing methods. However, long queues, registering procedures and traveling proved to be major challenges. To curb the spread of this virus government required diagnostic sensors that are timely, portable, and accurate POC so that more people could be tested [44].

There are diagnostic methods that are regarded as gold standards for detection of infectious diseases such as detection of TB and HIV using immunoassay and Covid-19 via PCR [73]. These diagnostic standards are regarded as low cost, extremely sensitive and easy to operate with low limit of detection [74]. However, the recent 2020 worldwide Covid-19 pandemic forced a divergence use of the traditional gold standards methods. The gold standards methods often requires a well-trained physicians and it is time consuming. The alternative testing such as lateral flow immunoassay and other plasmonic nano sensors significantly reduces the time for results down to 15 minutes with an added advantage of portability. Even though the detection limit of the gold standard methods is superior to the plasmonic nano sensors, there is a consensus prospects that these diagnostic nano sensors based on plasmonic nanoparticles would be use more in the future to reach masses for screening of infectious diseases [44].

5.2 Miniaturization

The optical biosensors often require a reliable light source and an optical read out instrument. The optical biosensors mostly relies on the natural sun light as the source of light and the human eye as the photo-detector in the visible wavelength. A good example of these optical biosensors are the colorimetric pregnancy tests [44]. Where the nanoparticles such as gold produces LSPR that induces light absorption change detectable by the naked eye. The future of this technology heavily depends on the development of semiconductor technology to produce extremely sensitive, reliable and enhance resolution results. The fast growing semiconductor technology in the cell phone industry means that cell phones are now equipped with powerful computing power and high resolution cameras. These cell phone capabilities means that in the future, the light emitted diode (LED) from cell phones, could be used as a light source with accurately controlled wavelength and intensity. The high-resolution camera of a cell phone could be used as sensitive photo-detectors for the sensing. Hence, in the future, cell phones would be used to provide real-time diagnostic results via analysis of optical signal analyzed with complex algorithms [44].

5.3 Theranostics

Theranostics is a nanomedicine that comprises of both diagnosis and therapies of illnesses achieved by using a biomaterial based nanoplatform. This nanomedicine technology uses nanostructures within the 1 to 100 nm range that are functionalised with organic or inorganic materials and often with an engineered compound such

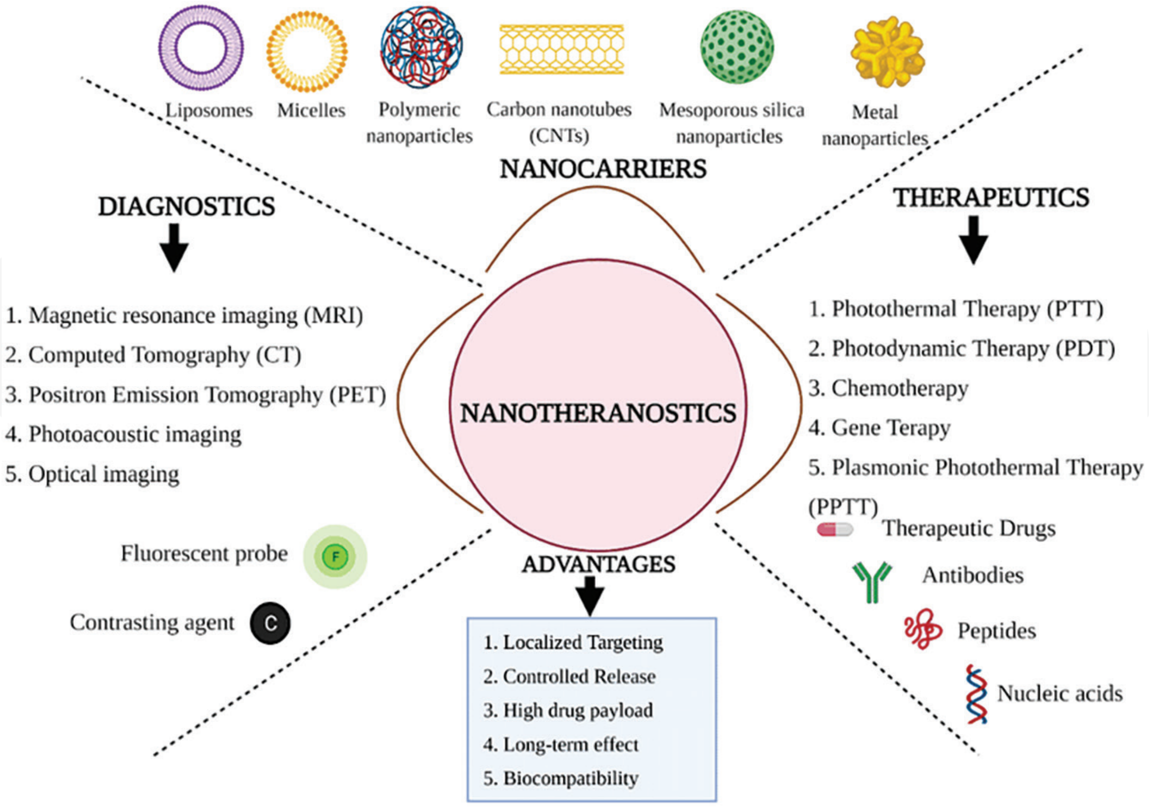

Figure 8.
Various therapies and diagnostic approaches used for the theranostic concept [75].

as phthalocyanine that could disrupt the functionality of the cells of the infectious disease [75]. The functional groups on the surface of the nanoparticles usually directs them to the desired location of the infectious disease that could be detected using ultrasound, MRI, or CT scans (diagnosis). Once at the target site, the engineered compounds are activated by energy source such as laser (phototherapy), causing them to release energy causing a cell destruction (therapy) such as stubborn cancer cells. The advantages of theranostics technology that would make this the technology of choice in the future are; improved targeting effect, reduced systematic toxicity and enhanced solubilizing potential to hydrophobic drugs [76]. **Figure 8** shows a schematic of the dual effects of theranostic approaches.

Even though application of plasmonic materials in bio-molecular sensing has seen great leaps in the past couple of decades and has circumvented multiple challenges. The areas that are leading the path into the future for the biosensing technologies is machine learning and artificial intelligence.

5.4 Machine learning

Plasmonic biosensors uses plasmonic nanoparticles to enhance the surface Plasmon effect, which highly depends on the morphology of the nanoparticles. The different morphology of these nanoparticles offer difference optical properties. Hence, it is crucial to design the plasmonic nanoparticles to suit its application [77, 78]. Difference morphology are often required for the detection of different infectious diseases such as human immunodeficiency virus (HIV), tuberculosis (TB), hepatitis B virus (HBV) with varying limits of detection. The various morphology of plasmonic nanoparticles is shown in **Table 1**.

The prospects of using plasmonic nanoparticles would depend on better understanding and accurate prediction of the plasmonic properties of the nanoparticles. Often optical properties of nanoparticles are computed using molecular modeling. However, it is challenging to predict with a high degree of accuracy the perfect nanoparticle morphology with the required optical properties. Furthermore, molecular modeling is time consuming [79, 80]. The recent developments of machine learning and artificial intelligence are the answer for this challenge and holds hope for future applications. Machine learning is more accurate in predicting the required properties for the application. Furthermore, machine learning has the capabilities to optimize the design parameters of the plasmonic nanoparticles to achieve the required optical properties [81]. Hence, machine learning serves as the powerful tool that can be used extensively in various plasmonic image analysis for better understanding their optical properties.

6. Conclusion

Plasmonic nanostructures with various morphologies have sparked interest for use in biomarker sensing and rapid diagnostics. Spherical plasmonic nanoparticles such as gold and silver have played an integral part of these technologies, however, in recent years other morphologies such as rods and nanowires have been of interest due to their high aspect ratios and high surface area. In this chapter, the fundamental plasmon properties were explored for various diagnostic and biosensing applications in infectious diseases and common water pathogens. We also explored the prospects for rapid diagnostics and biomarker technologies in a world that requires test results efficiently, reliably, and quickly. The fate of traditional diagnostic technologies was also discussed with some new developments that would help this technology soon.

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