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Research review paper

Plasmonic-based platforms for diagnosis of infectious diseases at the point-of-care

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ABSTRACT

Infectious diseases such as HIV-1/AIDS, tuberculosis (TB), hepatitis B (HBV), and malaria still exert a tremendous health burden on the developing world, requiring rapid, simple and inexpensive diagnostics for on-site diagnosis and treatment monitoring. However, traditional diagnostic methods such as nucleic acid tests (NATs) and enzyme linked immunosorbent assays (ELISA) cannot be readily implemented in point-of-care (POC) settings. Recently, plasmonic-based biosensors have emerged, offering an attractive solution to manage infectious diseases in the developing world since they can achieve rapid, real-time and label-free detection of various pathogenic biomarkers. Via the principle of plasmonic-based optical detection, a variety of biosensing technologies such as surface plasmon resonance (SPR), localized surface plasmon resonance (LSPR), colorimetric plasmonic assays, and surface enhanced Raman spectroscopy (SERS) have emerged for early diagnosis of HIV-1, TB, HBV and malaria. Similarly, plasmonic-based colorimetric assays have also been developed with the capability of multiplexing and cellphone integration, which is well suited for POC testing in the developing world. Herein, we present a comprehensive review on recent advances in surface chemistry, substrate fabrication, and microfluidic integration for the development of plasmonic-based biosensors, aiming at rapid management of infectious diseases at the POC, and thus improving global health.

1. Introduction

In today's healthcare landscape, infectious diseases persist as a concerning source of the global disease burden. Despite advances in health education, treatment regimens and diagnostic tools over the last few decades, there are clear indications that many health issues associated with infectious diseases still impact millions of people worldwide, as seen from their prevalence of over 3.1 billion cases and responsibility for roughly 15% of total deaths worldwide (8.2 million) in 2016 (Floyd et al., 2018; Naghavi et al., 2017; Vos et al., 2017). Furthermore, health initiatives in the developing world have recently uncovered new concerns that need to be addressed, such as significantly increased incidence and mortality from multi-drug resistant tuberculosis (TB) and HIV-1-associated TB (Laxminarayan et al., 2013; Mani et al., 2014; Wang et al., 2013). As such, there is a prevailing need for novel disease management strategies and tools to address the challenges and implications attributed to infectious diseases, particularly in the developing world (Lifson et al., 2016; Wang et al., 2016; Xu et al., 2015; Drain et al., 2014).

To effectively manage infectious diseases in resource-limited settings, rapid, simple-to-use, inexpensive diagnostics are highly sought after for POC testing. Although traditional diagnostics such as ELISA

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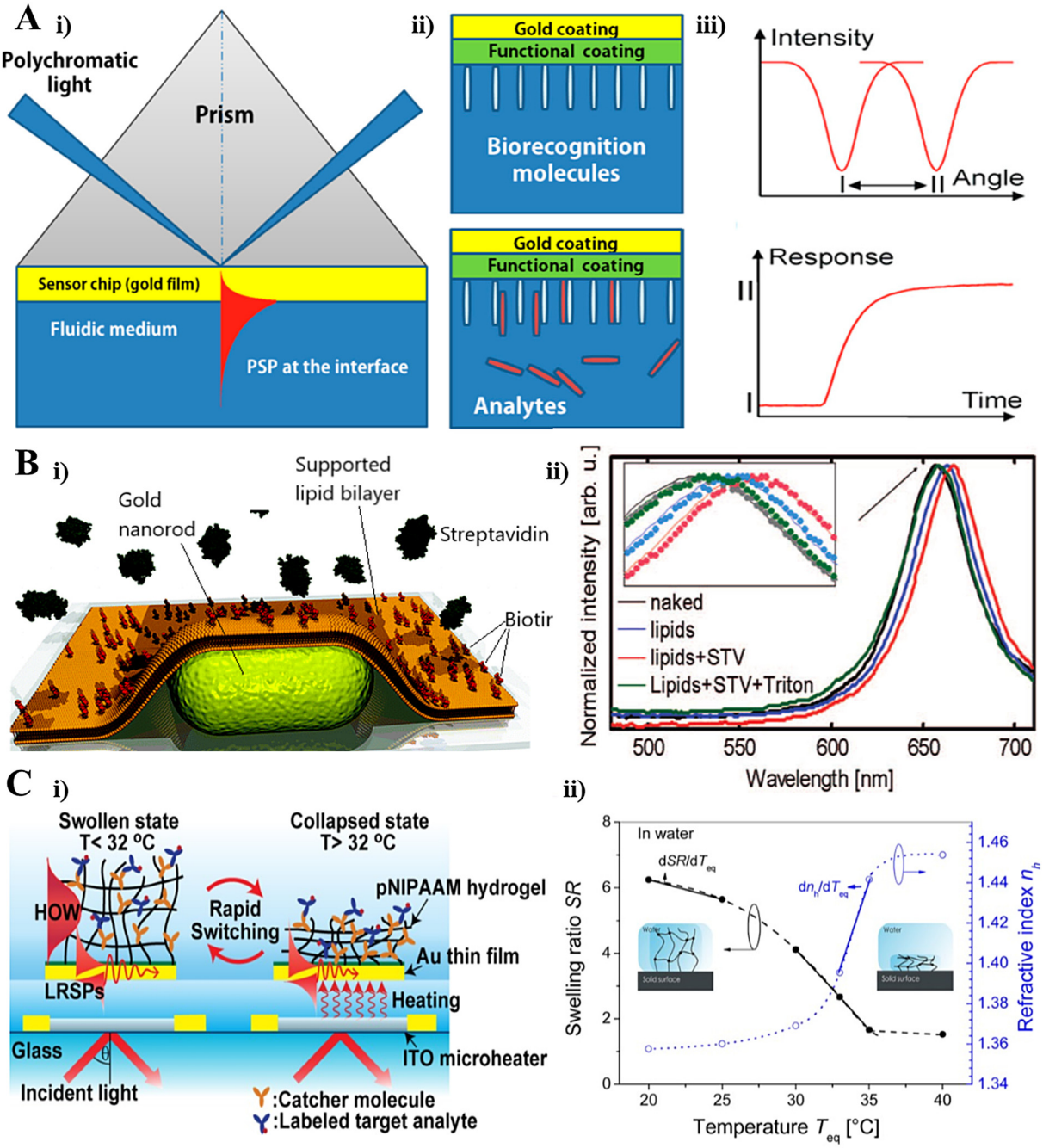


Fig. 1. Mechanism and recent advancements in SPR biosensing.
(A) Mechanism of SPR detection: (i) Schematic of SPR biosensor in the Kretschmann configuration. (ii) Functional coatings immobilize capture ligands for analyte detection in the sample. (iii) Typical sensor readouts (*i.e.,* resonance angle changes upon capture of the analyte). All figures adapted with permission from Nguyen et al., 2017 material reproduced under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0. (B) Supported lipid bilayer (SLB) coated over nanostructures for improved SPR sensing (i) Schematic of a gold nanorod coated with a biotinylated (red) lipid membrane (orange) for detection of streptavidin (STV) (dark green). (ii) Example scattering spectra for GNPs under various coating conditions. All figures adapted with permission from Baciu et al., 2008, Copyright 2008 American Chemical Society. (C) Polymer mediated platform using thermo-responsive tuning of the sensor surface (i) Schematic of thermal response and SPR setup using indium tin oxide microheater and tunable pNIPAAM hydrogel. (ii) The temperature-dependent swelling ratio and refractive index changes. All figures adapted with permission from Toma et al., 2013, Copyright 2013 American Chemical Society.

and PCR can provide reliable disease diagnosis and treatment monitoring, they suffer from the need for well-equipped facilities and skilled operators, rendering them unfeasible in resource-limited settings for POC testing. This has prompted a strong interest into diagnostic platforms that are applicable at the POC to facilitate early disease detection in all regions of the world (Shafiee et al., 2015b). With the growing need for these POC platforms, the World Health Organization (WHO) has created the ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and deliverable to end users) framework, outlining guidelines for their development (Mabey et al., 2004). Current POC solutions, such as lateral flow assays and paper-based devices, succeed in providing rapid, inexpensive and facile platforms, but are held back by inadequate sensitivity, selectivity and overall reliability, highlighting the challenges faced by POC diagnostics. As an imperative tool for disease management strategies in the developing world, POC diagnostics are continually improving to address the

shortcomings of current methods and become an instrument that can reliably be implemented all necessary settings.

Recently, plasmonic-based platforms have emerged as a key candidate in the development of next generation diagnostics to alleviate the burden of infectious diseases in the developing world. Leveraging the overlap between analytical chemistry and optics, plasmonic-stemmed modalities can enhance the performance of pre-existing platforms by providing stable, real-time, highly sensitive and label-free detection of analytes (Anker et al., 2008; Zarei, 2017). These analytes include various biomacromolecules such as proteins, lipids, exosomes/liposomes, nucleic acids and detection of whole pathogens in various complex biological media to diagnose a variety of infectious diseases (Jackman et al., 2017; Masson, 2017). Researchers have recently been able to further utilize and adapt the advantages of these plasmonic-based platforms in diagnostic strategies that both outperform and offer greater POC feasibility than gold standard methods. For example, de la Rica and Stevens (2012) were able to use plasmonic-enhanced ELISA to achieve sensitivities that were undetectable by gold standard NAATs. Even more recently, for the detection and quantification of the HIV-1 p24 antigen, using plasmonic platforms, Kosaka et al. (2017) were able to detect HIV-1 p24 antigens at less than a week after infection. Furthermore, with the shift in paradigm for POC diagnostics towards integration with microfluidics and smartphones capable of all-in-one functionalities, plasmonic biosensors have become increasingly important tools in field deployable diagnostics (Guner et al., 2017; Na et al., 2018; Preechaburana et al., 2012; Zhang and Liu et al., 2016; Zhou et al., 2013). As POC diagnostics constitute one of the major strategies in infectious disease management worldwide, plasmonic-based modalities have the potential to lower the burden of disease in the developing world.

In this perspective, we aim to address the gap in the current understandings of the underlying principles of plasmonic-modalities, recent advancements (*i.e.*, surface chemistry, nanofabrication, microfluidics) in academic settings and current applications in infectious diseases diagnostics (*i.e.*, HIV-1, hepatitis B, and tuberculosis). This review aims to facilitate future progress in POC-deployable diagnostics within resource-constrained settings. The mechanism of various sensing modalities (*i.e.*, SPR, LSPR, plasmonic colorimetric assays, and SERS) and the recent advancements in the fabrication, functionalization and biosensing strategies in order to achieve clinically relevant performances within POC feasible frameworks will be discussed. We also describe the existing applications for pathogen detection using these platforms and what needs to be improved in terms of design, complexity and sensitivity. Still, there are limitations and technical challenges in developing robust, clinically relevant plasmonic-based diagnostics capable of reaching the most-in-need, yet hard-to-access regions of the world. Thus, we lastly provide an overview of the future of these platforms, what needs to be overcome, and how plasmonic-based modalities continue to have an impact on diagnostics in the developing world for the management of infectious diseases.

2. Surface plasmon resonance (SPR)

2.1. Principles of SPR

The underlying principles of SPR biosensing have been reviewed extensively in many previous works and can be explained in summary as the propagation of surface plasmons along a metal-dielectric interface (*i.e.,* a noble metal such as gold and an aqueous medium as the dielectric) (Homola, 2008; Tokel et al., 2014; Zeng et al., 2014; Zhang and Liu, 2016). In biosensing applications, bioreceptors are first immobilized on the gold sensing surface using approaches such as physical absorption, covalent bonding and affinity-based absorption (Ravi Shankaran and Miura, 2007). The sensitivity, selectivity and overall performance of a platform relies heavily on the functionalization of this surface. Upon binding between the analyte and the immobilized ligand, the local refractive index changes, detectable through the change in the incident light needed to achieve the plasmon resonance condition (Šípová and Homola, 2013). As such, SPR biosensors are inherently refractometric devices that use measurements of the angle, wavelength, intensity or phase of incident light to achieve the detection and quantification of analytes (Fig. 1A) (Brolo, 2012).

The resonance condition itself is a result of incident light excitation inducing coherent oscillations of free electrons in the metal, resulting in surface charge oscillations, or propagating plasmons on the metal-dielectric interfaces (Jackman et al., 2017; Tokel et al., 2014). The exponential decay of the electric field in the direction normal to the interface results in evanescent waves with limited penetration depth in both media, typically on the order of half the incident wavelength (Brolo, 2012). When this evanescent field couples with the surface plasmon electric field by having the same frequency and wave vector, the produced resonance can be observed through a decrease in the reflected light intensity. This resonance condition is highly sensitive to changes in the refractive index of the dielectric medium, as the surface plasmon mode is altered (Homola, 2008; Zeng et al., 2017).

In addition, to satisfy energy and momentum constraints of the system, an optical coupling element with the incident light is required to excite the surface plasmons (Couture et al., 2013; Li et al., 2015). Prism coupling in the Kretschmann configuration, grating, waveguide, photonic crystal and fiber-optic coupling systems are often employed to achieve the momentum requirements for plasmonic excitation (Abdulhalim et al., 2008; Chien and Chen, 2004; Homola et al., 1999). The Kretschmann configuration is used in most conventional benchtop and portable SPR systems because of its stability and sensitivity, but other methods are being explored to achieve further miniaturization for POC implementations (Tokel et al., 2015).

2.2. Recent advancements in SPR biosensors

2.2.1. Surface functionalization

The design and fabrication of these sensing surfaces constitute the most important challenge in developing new SPR platforms that can match the performance of gold standard methods in a POC feasible framework. In this regard, surface functionalization of capture ligands, which directly influences the efficiency, selectivity and sensitivity, has been one of the major focal points of recent research in order to produce highly sensitive, easy-to-manufacture, and cost-effective SPR biosensors. Conventional surface functionalization techniques such as physical absorption, covalent bonding and affinity-based absorption are often limited by environmental factors, such as pH, temperature and ionic strength as well as the inability to precisely control orientation and obtain an even coverage of the sensing surface, ultimately leading to increased non-specific interactions, decreased sensitivity and loss of biological activity (Ravi Shankaran and Miura, 2007; Tokel et al., 2014). Newer materials and functionalization techniques enhance the specificity and sensitivity between the biomarker and the immobilized ligand. For example, supported lipid bilayers (SLB) have been employed to probe cellular interactions, offering dynamic and flexible biorecognition, preservation of native protein structures, and inherent antifouling properties (Fig. 1B) (Lee et al., 2013b; Tokel et al., 2014). The preservation of structure in receptors as a result of membrane embedment may be realized through these platforms, offering greater sensitivity through maintaining receptor activity, mimicking cellular signaling and increasing affinity to certain biomarkers (Inci et al., 2015a). For instance, the embedment of transmembrane G-protein-coupled receptors within these structures can be used to detect HIV-1 as they naturally facilitate entry into T cells (Debnath et al., 2013; Patching, 2014). Biosensor chips have also used hybrid systems with coated SLBs on nanostructures or nanotopographic substrates, using these hybrid structures as an attractive platform to investigate biorecognition events in an almost native environment due to their natural responses, such as lateral rearrangement of receptors, and higher multiplex potential

Table 1
Summary of SPR diagnostics for various infectious diseases.

Disease	Type of biomarker	Biomarker	Biorecognition element	LOD	Sample	Notes	Reference
HIV-1	Nucleic Acid	HIV-1 DNA	Hairpin DNA Capture Probes	48 fM	Buffer solution	Double-layered DNA tetrahedrons for signal amplification	Diao et al. (2018)
HIV-1	Protein	HIV-1 Protease	HIV-1 Protease Substrate	10 pg/mL	Buffer solution	Magnetic Beads Released on substrate cleavage	Esseghaier et al. (2013)
HBV	Nucleic Acid	HBV DNA	HBV DNA primers	2 fg/mL	Buffer solution	SPR used to measure refractometric changes in solution after LAMP	Chuang et al. (2012)
HBV	Protein	Anti-HbsAg	HbsAg	N/A	Serum Samples	Poly(HPMA-co-CBMAA) bottlebrush polymer surface	Riedel et al. (2016)
HBV	Protein	HbsAg	Anti-HbsAg	10 pg/mL	Buffer Solution		Choi et al. (2014)
TB	Nucleic Acid	RCA products of DNA targets	Padlock capture probe	8.2 ng/mL of clinical DNA	RCA product solution	Able to detect point mutations associated with drug resistant TB	Xiang et al. (2013)
TB	Nucleic Acid	RCA products of target rRNA sequence	AgNPs conjugated capture probe	20 aM or 10^4 CFU/mL	RCA product solution	Validated in clinical samples from sputum, urine, cerebrospinal fluid	Xiang et al. (2015)
TB	Nucleic Acid	PCR products of DNA target	Peptide Nucleic Acid Probe	0.26 pM	PCR product solution		Silvestri et al. (2015)
TB	Nucleic Acid	DIG-labelled PCR products	Anti-DIG	63 pg/mL	PCR Product Solution	OLED light source and validated in 600 clinical sputum specimens	Prabowo et al. (2018)
TB	Protein	CFP-10 secretory antigen	Anti-CFP	100 pg/mL	Artificial Urine		Zou et al. (2017)
TB	Protein	Ag85 secretory protein	Anti-Ag85	10 ng/mL	Buffer Medium		Trzaskowski et al. (2018)
Malaria	Protein	*Pf*GDH	DNA aptamer	0.7 pM	Undiluted human serum		Singh et al. (2018)
Malaria	Protein	*Pf*LDH	DNA aptamer	1.30 pM	Diluted human serum		Figueroa-Miranda et al. (2018)
Malaria	Protein	Heme	Apo-hemoglobin	2 μM or	Buffer Solution	Useful for diagnosis of hemolytic pathologies	Briand et al. (2012)

(Baciu et al., 2008; Lee et al., 2013b). In addition, by modifying the nanotopographical features, different curvatures of the SLBs may be obtained, allowing for natural, morphology-dependent electromagnetic "hotspots", resulting in increased sensitivity, tuning of site-specific absorption and better preservation of native receptor protein structures (see Fig. 1B) (Roiter et al., 2009).

Polymer-mediated systems such as hydrogels or bottlebrush polymer layers also offer advantages such as nanostructure hybridization, allowing versatile and multiple functionalization, thermo-responsive rapid tuning of the sensor surface, high capacity binding in a dynamic 3D biorecognition matrix, and anti-fouling properties (Jeong et al., 2009; Tokel et al., 2014; Toma et al., 2013). Using an indium tin oxide (ITO) microheater to control swelling of the hydrogel, Poly(N-isopropylacrylamide) (pNIPAAm) could be controlled (Fig. 1C). The implications of such a design allows for capture of analytes at a capacity and sensing volume much greater than current immobilized ligands, without compromising the bulk refractive index sensitivity, which decreases drastically away from the surface, by collapsing the hydrogel and bringing it close to the sensing surface. In addition, multiplexing can be realized through readouts from spatially separated sensing regions and specific collapse and swelling of certain regions (Toma et al., 2013). Low fouling surfaces are also essential for biosensors to achieve highly sensitive readouts. Current strategies mainly involve coatings of polyethylene glycol (PEG) derivatives, which are susceptible to oxidative damage and have limited non-specific blocking in real biological samples such as whole blood or serum. Zwitterionic hydrogels, self-assembled monolayers and bottlebrush architectures offer advantages such as easy and high capacity functionalization compared to PEG derivatives due to the abundance of carboxylic acid groups and ultra-low fouling ($< 5\ ng/cm^2$) maintained even in undiluted biological samples (Chou et al., 2016; Vaisocherová et al., 2015; Yang et al., 2009). These low fouling and dynamically tunable surfaces continue to be investigated to optimize their advantageous properties, and have been shown to have synergistic effects in improving the sensitivity of many reported platforms (He et al., 2018; Riedel et al., 2017; Wijaya et al., 2011).

2.2.2. Portability

Many recent designs have aimed to improve the portability of SPR-based biosensors, including miniaturization and optimization of microfluidics. For instance, a portable, clinically relevant biosensor was recently developed based on a smartphone platform using the screen as a light source and the front-facing camera as a sensor (Preechaburana et al., 2012). The disposable sensor allows for easier usage in decentralized settings and reduces the need for extra handling steps. Similarly, using a smartphone as the light source and analyzation hardware, Liu et al. (2015) created a fiber optic SPR sensing platform. The limit of detection (LOD) achieved with their setup was validated through a commercial device, despite being over 1,000 times less expensive and negligible in weight compared to it. With the elimination of sensitive, expensive and bulky optical components in conventional setups, the utility of smartphones as a provider for hardware and software requirements of a sensing platform combined with recent advancements in SPR biosensors could allow for widespread use in low-income communities.

Other obstacles limiting miniaturization are bulky liquid handling systems, high power consumption and relatively high sample volumes (Yager et al., 2006; Zhou et al., 2013). Optimization of microfluidic systems, such as the use of an electric-power-free pump and reduction of sample size using vertical focusing without compromising time and sensitivity has allowed for further advancements in portability. In their design, (Na et al., 2018) used a vacuum-drive pump in a palm-sized device to eliminate the need for electric-powered pumps. Also, a vertical focusing element was able to reduce the sample volume required, which is traditionally limited by microchannel size limitations and channel clogging. Designs similar to this self-contained platform, which

can further be coupled with smartphone light source and signal analysis can greatly improve the prospect of miniaturization without compromising performances, as optical and liquid handling systems constitute the major roadblocks to miniaturization.

2.3. Applications of SPR diagnostics

For summary of applications using SPR modalities, see Table 1.

2.3.1. SPR platforms for diagnosis of HIV-1

The detection of low quantities of viral copies is essential for early diagnosis before anti-HIV-1 antibody development and evaluating the efficacy of anti-retroviral treatment (ART), both of which can vastly improve the prognosis of the 36.9 million people living with HIV-1/AIDS worldwide (World Health Organization, 2018). Current portable platforms suffer from being expensive and slow with low throughput and sensitivity, making the global demand for HIV-1 POC diagnostics in resource-limited settings urgent, since the reliable and timely administration of ART becomes increasingly reliant on diagnostic technologies.

With SPR biosensors able to achieve low limits of detection, a recent platform developed by Diao et al. (2018) was able to obtain a 48 fM LOD of HIV-1-related nucleic acids using entropy-driven strand displacement reactions as an isothermal, label-free nucleic acid amplification method. In conjunction, nanostructured DNA tetrahedrons were used for SPR signal amplification. This platform has many advantages such as high sensitivity, stability, repeatability and rapid detection and can be easily applied to other DNA targets as well. As with many DNA methods, the extraction of DNA from biological samples can hinder their POC feasibility. Further validation in clinical samples is needed. However this platform shows promise in delivering highly sensitive and PCR-free detection of DNA.

Moreover, there are also combined assays integrating multiple sensing modalities on the same device. As an example, the researchers developed a system employing SPR, cyclic voltammetry and faradaic impedance spectroscopy to detect HIV-1 protease biomarkers for HIV-1 screening (Esseghaier et al., 2013). A 10 pg/mL limit of detection was achieved by evaluating the cleavage of magnetic beads linked with HIV-1 protease substrate peptide to the gold sensing surface. A significant shift in both electrochemical and SPR signal is then quantified. This platform is rapid and low-cost, and completes one assay in 25 min; however, it also lacks validation in clinical samples. Nevertheless, it was shown that drug screening and monitoring of inhibitory activity can also be performed using this platform. As such, personalized treatment along with diagnostics may be possible with deployment of similar platforms at the POC, ultimately optimizing care for each patient.

2.3.2. SPR platforms for diagnosis of Hepatitis B

Hepatitis can lead to deadly complications such as cirrhosis or liver cancer, with acute and chronic symptoms caused by hepatitis B virus (HBV) infection. Current gold standard PCR methods must be carried out in a laboratory setting to distinguish different etiological agents (Yildiz et al., 2015). In lieu of this, various strategies have been developed in recent years using SPR platforms for hepatitis diagnosis at the POC. Namely, Riedel *et al.* recently utilized poly[(N-(2-hydroxypropyl) methacrylamide)-co-(carboxybetaine methacrylamide)] (poly (HPMA-co-CBMAA) bottlebrush polymeric structures on top of a gold-coated glass substrate (Riedel et al., 2016). Immunogenic immobilization ligands were further biofunctionalized on these bottlebrush structures. The antifouling properties of these polymer-mediated biointerfaces were previously discussed in Section 2.2. Surface initiated radical polymerization allowed selective functionalization of the bottlebrush functional groups to not compromise the antifouling properties due to over-conjugation. Coupled in an optical fiber configuration, this platform was used to detect hepatitis B virus surface antigen (HbsAg) in diluted clinical plasma samples that validated clinical diagnosis and outperformed ELISA methods. On the other hand, an interesting approach to improve sensitivity, and hence the employability of SPR-based POC platforms, was presented by Choi et al., where plasma treated parylene-N film was deposited on a gold covered glass substrate (Choi et al., 2014). Through enhancing receptor antibody immobilization for HbsAg detection, a 1000-fold increase in sensitivity (LOD of 10 pg/mL) was reported over conventional ELISA. As such, immunogenic biorecognition coupled with detection using an SPR platform present sensitive and rapid platforms for early diagnosis of HBV.

In contrast, DNA-based methods have also been explored and have shown similar promise in delivery of POC diagnostics for hepatitis. For example, (Chuang et al., 2012) used SPR sensing to measure refractive index changes in a sample after loop-mediated isothermal amplification (LAMP). LAMP has shorter amplification times and higher efficiency and has become preferred in field-friendly applications. Refractometric measurements using a SPR sensing platform were taken of the sample before and after amplification to quantify viral DNA. In this particular platform, 2 fg/mL of HBV DNA was detectable in 17 min, making DNA-based SPR platforms ideal for ultra-low viral copy detection. Continual development of DNA methods may allow for devices with inline DNA extraction of crude sample inputs, due to specificity of amplification reagents and sensitivity of the assay results. Still, the need for pre-processing of biological samples currently stands in the way of widespread deployment of DNA-based SPR methods, despite their high sensitivity.

2.3.3. SPR platforms for diagnosis of Tuberculosis

Tuberculosis (TB), caused by the pathogen *Mycobacterium tuberculosis*, is the leading opportunistic infection in HIV-1 patients, resulting in significant morbidity and disease burden in the developing world. Currently available diagnostics include latent *M. tuberculosis* diagnostics, such as the tuberculin skin test and interferon gamma release assays, and TB disease diagnostics such as the most commonly used sputum smear microscopy and gold standard culture/molecular methods. Low sensitivity and specificity and high cost, turnover time and skill requirements add complicating factors to the current landscape of TB diagnostics, which consists of diagnosing disease-progressed TB from latent infections and identification/management of antibacterial resistance (Cobelens et al., 2017; Dheda et al., 2013; Mani et al., 2014; McNerney and Daley, 2011; Wang et al., 2013).

In compliance with the ASSURED requirements, SPR biosensors able to distinguish active TB infections through various biomarkers eliminate the need for expensive labels, cut down skill dependence in obtaining accurate results and drastically decrease test turnover time (McNerney and Daley, 2011; Zou et al., 2017). For example, (Trzaskowski et al., 2018) developed a portable SPR device with a limit of detection of 10 ng/mL or 1×10^4 CFU/mL using antibody responses to the Ag85 secretory protein. The platform was comparable to a commercial benchtop SensiQ Discovery SPR system and validated in real TB patient sputum samples. In another study, using an organic light-emitting-diode (OLED) prism-coupled SPR system, (Prabowo et al., 2018) was able to obtain a 63 pg/mL LOD for IS6110 DNA targets in a highly sensitive (98.4%) and specific (96.6%) platform able to analyze clinical samples. The digoxigenin (DIG) labelled PCR products of the DNA target were quantified using SPR. The use of OLEDs as a lightweight alternative to laser-based or halogen lamp systems allows for the portability of device, along with the superior color contrast, long life-time and low power consumption.

Furthermore, the ability to differentiate TB and non-TB *Mycobacterium* is another strategy for drug resistance management and effective treatment. A sensitivity of 100 pg/mL was achieved in a prism-coupled system by (Zou et al., 2017) detecting the early secretory antigen CFP-10 which is specific to TB mycobacterium. An immunoassay along with magneto-plasmonic NP signal amplification was used to detect the TB biomarker in urine samples, which are ideal samples

because of their ease of collection and little need for preprocessing. Furthermore, other promising and highly sensitive nucleic acid detection methods have been reported to manage antibacterial resistance, including an inline isothermal rolling cycle amplification (RCA) system for differentiation of TB strains from non-TB strains by (Xiang et al., 2015), another RCA system for detection of point mutations associated with multidrug resistant *M. tuberculosis* (Xiang et al., 2013), and a grating-coupled SPR sensor with high miniaturization and multiplex potential by (Silvestri et al., 2015).

2.3.4. SPR platforms for diagnosis of Malaria

In the global perspective for malaria management, rapid and accurate detection can be the difference between life and death, as well as reduces unnecessary expenditure of antimalarials, minimizing resistance and extending the lifetime of antimalarials (Yager et al., 2008). To address this, the detection of a malarial biomarker *Plasmodium falciparum* glutamate dehydrogenase (*Pf*GDH) was accomplished using single stranded DNA aptamers as capture probes for the *Pf*GDH antigen as published by (Singh et al., 2018). This SPR platform showed high specificity versus other malarial biomarkers and was able to detect 0.77 pM concentrations in serum using a capacitance-based electrochemical impedance signal transduction sensor. In another DNA aptamer impedance spectroscopic method, *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH) was robustly detected in variable pH conditions on a regeneratable SPR biosensor (Figueroa-Miranda et al., 2018). A 0.84 pM limit of detection was achieved in diluted serum in less than an hour per test. For this platform, limiting intermediary processing steps such as serum extraction or dilution needs to be investigated. On the other hand, an interesting method was investigated by (Briand et al., 2012) with the aim of detecting elevated levels of heme in blood. This biosensor uses the heme binding pocket of apo-hemoglobin in hemoglobin-polyacrylic acid conjugates forming nanonetworks. The limit of detection was 2 μM in buffer, which is clinically relevant as hemolytic pathologies such as malaria typically result in elevated levels in the range of 1–50 μM, making this platform suitable for potential whole blood diagnostics at the POC.

3. Localized surface plasmon resonance (LSPR)

3.1. Principles of LSPR

LSPR is another optical phenomenon caused by the interaction of light and discrete metallic nanoparticles (Jackman et al., 2017). The incident light induces collective oscillations of free conduction-band electrons, greatly increasing the intensity of the electric field at the sensor and creating a characteristic extinction peak at the plasmonic resonance frequency. Unlike SPR-based biosensors, the surface plasmon field is not propagating; instead, it is localized around the sub-wavelength nanoparticle (Brolo, 2012). Upon analyte attachment to the nanoparticles, the refractive index change causes a wavelength shift in the extinction spectrum, making LSPR platforms suitable for detection and quantification of biorecognition events (Fig. 2A) (Chen et al., 2015).

Using lithographic techniques, surface coating, and nanoparticle morphology, the plasmonic resonance frequency can be finetuned for particular applications. Commonly used materials are gold, silver and aluminum due to their inertness and tunable plasmonic properties. The morphology of the metallic nanoparticles also has effects on the spectral properties. For example, nanorods with a higher aspect ratio are much more sensitive to refractive index changes but compromise surface sensitivity due to longer surface decay lengths (Kelly et al., 2003). Increasing the edges, smoothness and symmetry on each discrete structure allows for tailoring of the LSPR response even further (Petryayeva and Krull, 2011). As such, LSPR offers a versatile, tunable and potentially portable platform that is simple, robust and can be readily implemented in POC diagnostics.

There is no need for a light coupling mechanism, so incident broad-spectrum EM radiation and spectrometer analysis of transmitted light represent the most typical measurement approach (Jackman et al., 2017). Angle-resolved and reflection-based refractive measurements can also be employed, but they are less common. These measurement strategies can increase bulk refractometric sensitivities and the figure of merit, at a tradeoff of a more complex design (Kravets et al., 2013; Lodewijks et al., 2012).

In LSPR platforms, the surface decay length is much smaller than SPR sensor chips, meaning the refractometric measurements resulting from changes of the refractive index need to be assessed much closer to the sensing surface (Fig. 2A) (Brolo, 2012). Thus, the refractometric sensitivity can be up to an order of magnitude less than SPR counterparts due to this large difference in sensing volume (Brolo, 2012; Willets and Van Duyne, 2007). However, in many cases, the design of the sensing platform has allowed for equivalent if not better sensitivities due to better responses closer to the sensing surface. In the current landscape where Kretschmann prism-coupled SPR sensors represent the most studied and commercialized products, LSPR sensors capable of achieving the same sensitivities have advantages due to their simpler design, thermal stability and portability (Brolo, 2012; Mayer and Hafner, 2011; Tokel et al., 2014).

3.2. Recent advancements in LSPR biosensors

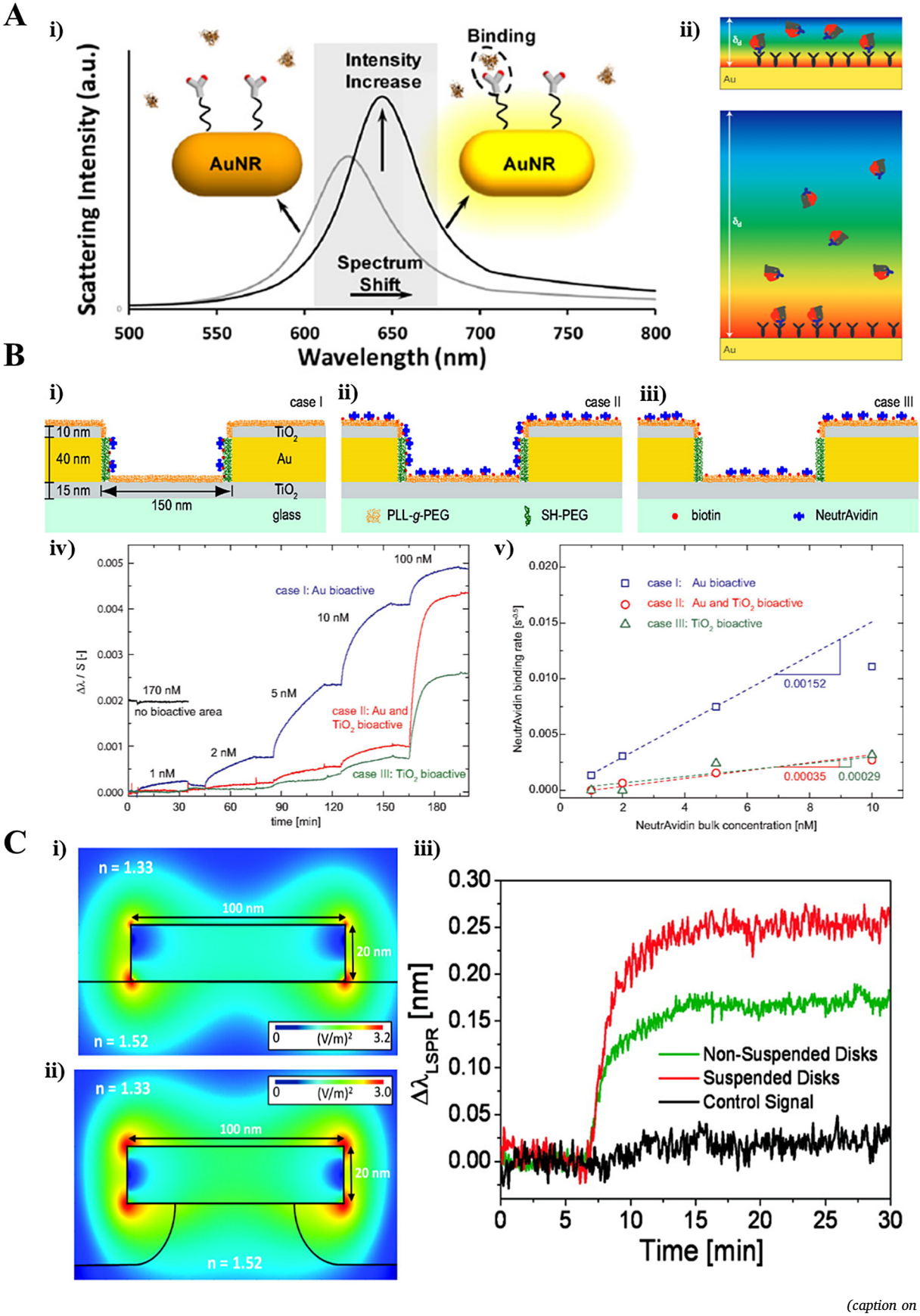
3.2.1. Surface functionalization

Functionalized layers on the surface can often employ new, highly specific binding ligands in conjunction with antifoulants. For example, aptamer-based ligands have been recently employed as sensing ligands as they are smaller than conventional antibody counterparts, and as a result is more sensitive as refractometric changes happen closer to the sensing surface (Unser et al., 2015). These platforms have also been recently explored for their sensor regeneration in protein detection using specific proteases and high specificity to DNA capture targets (Liu and Huang, 2012; Rosman et al., 2013). Supported lipid bilayer structures have also developed for LSPR substrates, where nanostructures facilitate binding native protein structure through replicating natural curvature, as well as enhance the electromagnetic field at places such as edges or corners (Galush et al., 2009).

Functionalization of antifouling agents as previously discussed in Section 2.2 such as poly/oligo ethylene glycol, saccharide-based, peptide-based and zwitterionic materials are also investigated to create highly specific and sensitive sensor surfaces (Boyer et al., 2009; Chen et al., 2009; Fyrner et al., 2011; van Andel et al., 2017). Other strategies are utilizing conformation changes in binding events, size specificity and shape complementation to distinguish between target analytes and unwanted interactions (Hong et al., 2011; Unser et al., 2015).

3.2.2. Lithographic methods for fabrication of sensing surfaces

Novel lithographic methods are also able to greatly reduce unspecific interactions. For example, (Otte et al., 2011) presented a wet-etching method to undercut Au nanodisks, creating pillar-like nanostructures capable of decreasing nonspecific binding of short DNA targets by around 41% (Fig. 2B). The basic principle of this approach is to minimize adverse effects from the overlapping LSPR signal upon non-specific interactions with the substrate as well as minimizing the effect from the high refractive index substrate itself. (Aćimović et al., 2017) were able to further optimize this approach through complete electromagnetic field decoupling between the plasmonic structures and the substrate to differentiate between nonspecific and targeted binding. Thus, more of LSPR signal during biorecognition events can be attributed to the target analyte versus nonspecific binding onto the substrate generating signal noise. It was reported that the bulk RI sensitivity was increased two-fold, the nonspecific absorption was reduced by a factor of 4–5 and 25% improvement in analyte sensitivity was observed. This platform is also reported to be easily and inexpensively fabricated using



(caption on next page)

Fig. 2. Mechanism and recent advancements in LSPR biosensing.
(A) Mechanism of LSPR detection: (i) Schematic of the LSPR mechanism. Adapted with permission from Chen et al. (2015), Copyright 2015 American Chemical Society. (ii) Differences in the surface decay length, δd, of LSPR sensing surfaces (top) and SPR sensing surfaces (bottom). Adapted with permission from Brolo, 2012, Copyright 2012 Nature Publishing Group. (B) Selective immobilization of biotin using PEG and thiol-based surface chemistry: (i) Only the highly sensitive Au section is functionalized. (ii) The entire surface is rendered bioactive. (iii) Only the less sensitive TiO_2 section is functionalized. (iv) Realtime wavelength shifts upon subsequent injections of increasing concentrations of NeutrAvidin under different surface functionalization conditions. (v) Increased binding rate based on specific surface functionalization. Adapted with permission from Feuz et al., 2010, Copyright 2010 American Chemical Society. (C) Improved sensitivity from suspended Au nanodisks: Magnetic field distributions of (i) nanodisks fabricated directly on a substrate and (ii) suspended nanodisks (bottom). (iii) Differences in the sensitivity of DNA hybridization based on the LSPR peak shift. Adapted with permission from Otte et al., 2011, Copyright 2011 American Chemical Society.

PDMS stamps and can be very easily integrated with microfluidic systems to obtain multiplexed, rapid and efficient readouts with little sample volumes.

3.2.3. Morphology of nanostructures

Different morphologies of the nanostructures have also been investigated to achieve high tunabilty and selectivity. Based on these designs, the specialized geometry allows for site-specific immobilization of receptors to so called “hotspots” where the shape-dependent uneven EM field is particularly strong, such as at sharp tips and edges (Dahlin et al., 2013). Binding at these sites have more pronounced LSPR signal readouts and are less affected by signal changes from binding at other locations, overall resulting in increased sensitivity. These designs can also combine the benefits offered by thiol-based immobilization techniques, which offer flexibility in length and saturation degree, with the properties of these specialized geometries. For example, thiol-based immobilization can selectively functionalize the edge of “hotspots” of gold nanoplates due to steric favourability (Fig. 2C) (Feuz et al., 2010; Gan et al., 2011). Recent interesting applications include the synthesis of gold “nano-shurikens” with enhanced sensitivity at each of its four tips (Zhang et al., 2017). Cylindrical designs have also been employed, with a platform showing that periodically varying height of gold nanocylinders can enhances the LSPR signal by a factor of 1.32 (Chamuah and Nath, 2015). To add, highly sensitive, fine-tunable gold-coated silica nanocylinders were fabricated using a lithography-free method, showing promise for continual development towards POC feasible LSPR-based biosensors (Thilsted et al., 2016).

3.3. Applications of LSPR diagnostics

For summary of applications using LSPR modalities, see Table 2.

3.3.1. LSPR platforms for diagnosis of HIV-1

As mentioned previously, the gold standard for the critical early detection of HIV-1 is through NAATs. To circumvent cost-prohibitive and high operator skill requirements, LSPR sensors have the potential to provide the sensitivity of NAATs in simpler formats. For example, a hybrid nano-mechanical and plasmonic sensor was developed by (Kosaka et al., 2017) that can be miniaturized and cheaply produced. Gold nanoparticles were employed as plasmonic and mechanic labels in this immunological sandwich assay for HIV-1 p24 protein antigen. For the nanomechanical transduction methods, the mass of the gold nanoparticles, which are directly related to the amount of antigen captured, was determined based on the vibrational modes and measured using the scanning optical deflection technique. For plasmonic quantification of the captured antigen, the substrate can be an optical cavity, allowing for the couple of optical cavity modes and the localized surface plasmon modes and thus creating hybrid plasmonic supermodes that can significantly enhance the scattering of the nanoparticles (Schmidt et al., 2012). The sensitivity achieved through this design is a significant step up from even the latest generation of gold standard methods, about a 5 order of magnitude and 2 order of magnitude improvement over immunoassays and nucleic acid amplification tests respectively, achieving detection as low as 10^{-17} g/mL or 0.1 copies per mL of serum, allowing detection as early as 1 week after infection (Cohen et al., 2010; Kosaka et al., 2017; Pilcher et al., 2007).

In another platform developed by (Inci et al., 2013), intact virions from unprocessed, whole blood was detected at a tradeoff for some sensitivity. They were able to successfully detect multiple subtypes of HIV-1 (A, B, C, D, E, G) using immobilized antibody capture probes against surface the gp120 envelope protein. The performance of this platform was best for quantification of subtype D. The limit of detection was reported as 98 ± 39 copies/mL and 85–99 % repeatability in extinction measurements. Overall this platform may be a potential candidate for field-friendly diagnostics due to its ability to detect and quantify HIV-1 viruses in whole blood. Further optimization of the sensing surface, such as utilizing hotspots or antifouling agents, could allow for clinically relevant detection of multiple HIV-1 subtypes using this platform. Comparatively, the latest generation gold standard nucleic acid amplification tests can detect within 10^{-18} viral copies/mL, a concentration reached around 2 weeks after infection, calling for even more sensitive LSPR detection to improve prognosis and reduce transmission.

Various other LSPR-based optical immunosensors have been employed for early HIV-1 detection applications. Through a facile electrochemical deposition fabrication method on an indium tin oxide (ITO) glass substrate, a uniform nanopattern was fabricated using gold nanodots (10–20 nm) for use as an LSPR sensing chip. This design by Lee et al. (2013a) used gold-thiol orientation specific immobilization of antibodies for capture and detection of gp120 HIV-1 protein. Absorbance measurements were taken using a UV-Vis spectrometer, achieving 200 fg/mL detection using cell culture supernatant. This method can be further optimized for POC applications by validating detection in relevant biological samples, decreasing costs as ITO glass substrates are quite expensive, and improving overall portability.

3.3.2. LSPR platforms for diagnosis of Hepatitis B

For hepatitis B, hepatitis B surface antigen (HBsAg) is one of the first biomarkers detectable, with the diagnosis cut-off around 0.07–0.12 ng/mL (Kao, 2008; Mukherjee, 2010). To satisfy the need for rapid POC diagnostics for HBV, (Kim et al., 2018) were able to demonstrate the use of a colloidal gold nanoparticle (GNP) immunoassay platform to detect HBV with a LOD of 10 pg/mL and 100 fg/mL for single-layered and sandwich assay respectively. HBsAg were captured on GNPs synthesized on a glass substrate, and a further layer of GNPs conjugated with the captured analyte was used for signal amplification. These results were validated in spiked human serum samples, showed high specificity against other antigens, and can be run in 10–15 min.

Furthermore, Wang et al. (2010) also exploited the LSPR characteristics of gold nanorods (GNR) for detection of HbsAg in both human serum and plasma. The GNRs were functionalized with monoclonal hepatitis B surface antibody in a facile method through simple physical absorption. They reported a limit of detection of 0.01 IU/mL (equivalent to around 4.3 fg/mL) in Tris buffer and validation with ELISA-diagnosed plasma and serum clinical samples.

On the other hand, Zheng et al. (2010) have investigated genetically engineered proteins as immobilized binding ligands compatible in LSPR biosensors. In this approach, gold-binding polypeptide was fused with HBsAg binding ScFv fusion protein. This method offers advantages such as directionally directed surface functionalization, better preservation of recognition element structure by mediating contact with the solid substrate surface, easy immobilization onto the gold sensor surface and

Table 2
Summary of LSPR diagnostics for various infectious diseases.

Disease	Type of biomarker	Biomarker	Biorecognition element	LOD	Sample	Notes	Reference
HIV-1	Nucleic Acid	HIV-1 DNA	HIV-1 DNA Capture Probe Functionalized on AgNPs	195 pM	Buffer solution		Liu and Huang (2012)
HIV-1	Protein	p24 protein antigen	Antibody	0.1 copies per mL	Undiluted human serum	Hybrid plasmonic and mechanical sensor	Kosaka et al. (2017)
HIV-1	Protein	gp120 protein	Antibody	98 ± 39 copies/mL	Undiluted whole blood	Whole virion detection	Inci et al. (2013)
HIV-1	Protein	gp120 protein	Antibody	200 fg/mL	Cell culture supernatant		Lee et al. (2013a)
HBV	Protein	HbsAg	Antibody	100 fg/mL	Human serum	AuNP signal amplification strategy was used	Kim et al. (2018)
HBV	Protein	HbsAg	Antibody	4.3 fgmL	Buffer solution	Validated in both ELISA-diagnosed clinical plasma and serum samples	Wang et al. (2010)
HBV	Protein	HbsAg	HbsAg binding fusion protein	100 pg/mL	Buffer solution		Zheng et al. (2010)
TB	Protein	CFP10-ESAT6 antibody	CFP010-ESAT6 fusion protein	N/A	Diluted human serum	Clinical samples validated with this platform	Sun et al. (2017)

high sensitivity (LOD of 100 pg/mL). These platforms are promising and can reliably provide early diagnostics far below the diagnosis cut-off concentration, but the cost and ease of large-scale manufacturing of these sensor surfaces may hinder actual development of field-friendly diagnostics incorporating these technologies.

3.3.3. LSPR platforms for diagnosis of Tuberculosis

To combat TB globally, many fronts of attack are needed, including drug resistance screening, identifying at risk individuals with compounding immunodeficiencies and accurately diagnosing TB infections early. Many recent platforms have been developed for diagnosing latent TB infections through LSPR detection of biomarkers, allowing better monitoring of immunocompromised individuals and communities to predict and manage outbreaks (Chuang et al., 2015; Peláez-Gutierrez et al., 2016). Few LSPR-based biosensors have been explored for early active TB diagnostic applications. Because of the high incidence and mortality in HIV-1 positive individuals, accurate, rapid diagnosis is imperative in regions with high disease burden. As such, (Sun et al., 2017) have incorporated gold nanorods functionalized with CFP10-ESAT6 fusion proteins in a LSPR biosensing platform. Here, they were able to establish a rapid and simple method for determination of the anti-CFP10-ESAT6 antibody. This platform was validated in clinical samples by incubation of diluted serum from TB positive and negative patients. Although this method has similar performance to ELISA, PCR methods still perform better at a tradeoff of higher complexity.

Moreover, the discovery of *M. tuberculosis* nucleoid-associated proteins such as Lsr2 and their role in drug resistance can allow for future development of biosensing platforms able to not only diagnose TB infection but identify effective treatment regimens (Golichenari et al., 2018; Gordon et al., 2010). Owing to the high sensitivity of LSPR-based TB diagnostics, it would be worth monitoring the global status and and detecting TB resistant strains. These drug resistance assays have already been explored in paper-based microfluidic devices, and utilizing LSPR platforms can increase accuracy and performance (Boehle et al., 2017).

4. Plasmonic colorimetric assays

4.1. Principles of plasmonic colorimetric assays

Arguably, plasmonic colorimetric diagnostics platforms are the most applicable and field-ready to be used in a POC environment. Relying on change in colour as a detection platform, colorimetric-based assays have been sought after for their simplicity in producing a signal output visible to the naked eye (Tang and Li, 2017; Wei et al., 2015). A common example of a widely used diagnostic method is colorimetric ELISA, which utilizes enzymes to trigger the oxidation of chromogenic molecules, inducing a colour shift in solution visible to the naked eye or quantified by UV-Vis spectroscopy. However, current colorimetric platforms suffer from a number of limitations, namely a lack of low-level sensitivity necessary for the early detection of bacterial and viral pathogens (D. Howes et al., 2014; Yang et al., 2016; Zhou et al., 2015). To combat this, Ag and Au nanoparticles have commonly been implemented within colorimetric devices due to their unique and advantageous optical properties (D. Howes et al., 2014; He et al., 2013; Song et al., 2011; Tang and Li, 2017; Wei et al., 2015). With their plasmon resonance properties, plasmonic nanomaterials are opening up new opportunities for colorimetric sensors that can combat the shortcomings of current designs.

The principles of plasmonic colorimetric devices rely on their localized surface plasmon resonance (LSPR) as covered in Section 3 to be able to induce a change in colour at a lower sensitivity than traditional colorimetric devices. The enhanced electromagnetic fields caused by the LSPR of Ag and AuNPs produce an enhanced absorbance peak in the visible and NIR range, which is detectable by the naked eye. The oscillations of these nanoparticles are influenced by many factors, including their size, shape, aggregation state, composition and other

external stimuli such as pH and refractive index (D. Howes et al., 2014; Haes et al., 2005; Stuart et al., 2005; Tang and Li, 2017; Wei et al., 2015). This allows their optical properties to be easily modulated to bring upon a change in colour in the presence of intended targets. The enhanced electromagnetic fields produced by Au and AgNPs coupled with the ability to easily tune their properties, making plasmonic colorimetric sensors a promising detection platform going forward.

There are two general methods to carry out the colorimetric assay. The first mechanism is the facilitation of the assembly (or disassembly) of nanoparticle aggregates. Functionalization of nanoparticle surfaces allows for necessary molelcular interactions to induce nanoparticle aggregation. Nanoparticle aggregation causes surface plasmon coupling within the aggregates, shifting the LSPR band and resulting in a colour transition (Tang and Li, 2017; Wei et al., 2015). This method takes advantage of the sensitive distance-dependent LSPR to be able to detect and quantify a variety of targets such as metal ions, living cells, proteins and small molecules. The molecular interactions used to tune the aggregation states of the nanoparticles include electrostatic interactions, hydrogen bonding, hydrophobic forces, and specific biomolecular interactions such as DNA hybridization (Boles et al., 2016; Borges and Mano, 2014; Yakoh et al., 2018; Zagorovsky and Chan, 2013).

The second mechanism used for colour transition is the chemical alteration of the shape, morphology or composition of the nanoparticles. As mentioned, the shape of nanoparticles influences their LSPR bands and associated changes in shape or length can cause a corresponding LSPR shift. This alteration is most commonly achieved through the use of an etchant that causes the oxidation of the nanoparticles, leading to a change in nanostructure (Tang and Li, 2017). The etchant is commonly activated within the presence of the target. These sensors are also known as “non-aggregation sensors” and can similarly be used to detect small molecules, metal ions, proteins and nucleic acids (Tang and Li, 2017; Wei et al., 2015; Yu et al., 2017). Below, we summarize their application and abilities in the detection of pathogenic disease biomarkers.

4.2. Recent advancements in plasmonic colorimetric assays

As with many biodetection methods, plasmonic colorimetric methods are constantly improving in terms of sensitivity, accuracy, speed, convenience and stability. There are a variety of recent papers that reflect this such as Guo *et al.* who proposed a plasmonic ELISA capable of changing to two different colours for more accurate quantification of biomarkers (Guo et al., 2016), Valentini and Pompa who used a one-step PCR method to increase sensitivity to 0.01 zeptomoles of HIV-1 template DNA (Valentini and Pompa, 2016), and Liu et al. who developed a simplified, wash-free colorimetric immunoassay (Liu et al., 2016). However, within this section, we here highlight the efforts made to adapt plasmonic colorimetric designs in a POC environment. Due to the facile concept of colour change detection, the potential of POC applications is easy to understand and has resulted in progress in paper-based devices, smartphone detection and multiplex capabilities.

4.2.1. Paper-based devices

Paper-based devices are a front runner for increased future POC research due to their simplicity, ease of use, disposability and easy general manufacturing. Combined with the quick, facile use of colorimetric detection, these sensors have large potential in the field of POC diagnostics. Detection within paper can be achieved through a variety of methods.For example, (Shafiee et al., 2015a) produced an ultrasensitive paper-based plasmonic colorimetric device for the detection of *E. coli* and *Staphylococcus aureus* (Shafiee et al., 2015a). AuNPs were incorporated onto cellulose paper and functionalized with a variety of recognition agents to bind the bacteria and create aggregates, resulting in colour transition. Using a smartphone for quantitative analysis, an LOD of 8 CFU/mL was established. Certain advantages of this final product included inexpensive materials, portability, ease of use and disposability, all while being detected by the naked eye. Multiplexing and sensitivity were also proven as *E. coli* and *S. aureus* were tested simultaneously and only resulted in a colour change based on the respective binding agents that were in solution. This proof-of-concept paper-based device is a needed step forward for a facile, cheap, and quick assay platform going forward and brings the possible advantage of thermal stability.

The theme of portability, simplicity and ease of use is continued in more recent studies as well. Yakoh et al. proposed a paper-based diagnostic device for monitoring chlorine ions with the use of silver nanoprisms (AgNPrs) (Yakoh et al., 2018). This was a simple, portable, disposable platform that utilizes paper to extend the device for better POC application. A colour transition was caused as a result of the oxidation of AgNPrs by oxygen, altering the size of the nanoparticles. In the presence of Cl^-, oxygen could not continue this oxidation and therefore were not reduced in size resulting in no colour shift (Yakoh et al., 2018). Their design consisted of circular, hydrophilic wax paper spots used to contain the sample and AgNPrs solutions. However, a large issue with paper-based devices is the lack of high sensitivity which is essential to pathogen detection, as neither of these designs produced results adequate enough for viral diagnostics (Zhao et al., 2008).

This challenge of sensitivity has not gone unnoticed. Recently, Albapatio *et al.* proposed a rather straightforward answer to the question of paper-based sensitivity. Their study was able to show that the LOD of plasmonic paper-based biosensors can be lowered by the simple alteration of performing the assay on a folded piece of paper (Alba-Patiño et al., 2018). Their design consisted of an accordion-shaped porous paper sensor that allows each drop of antibody and reagent to drop through multiple layers of the matrix. This results in several visible colorimetric signals which can be seen as a combined, intense signal that has the ability to benefit the LOD by a factor of 10. This is a very simple addition to paper-based devices that may have a very positive impact on the sensitivity of paper-based sensors (Liu et al., 2014a). Nevertheless, future work still needs to be performed regarding the reproducibility and sensitivity of these paper designs, as many suffer from outside interference as well as differences in paper manufacturing (Alba-Patiño et al., 2018; Yakoh et al., 2018; Zhao et al., 2008).

4.2.2. Smartphone detection

Although human eye detection is the most convenient avenue for diagnostics, when using colorimetric assays, it leaves a lot of room for interpretation error. Whether this be the inability to detect minute changes in the colour or differences in interpretation between people, smartphones can ultimately be called upon to help overcome these challenges. Being a high-level device that many have access to, even in low-resource areas, they become a popular field of interest for real-time, POC diagnostic technologies, including colorimetric assays. An example of this is Amirjani and Fatmehsari’s colorimetric plasmonic device that uses a smartphone for real-time detection of ammonia with the use of AgNPs (Amirjani and Fatmehsari, 2018). Through RGB (red, green, blue) value extraction, a linear range of 10–1000 mg/L was reported with an LOD of 200 mg/L upon the colour shift due to ammonia. This was further exemplified by a 92–112% recovery rate when testing their design within tap and purified water. Misra *et al.* used smartphone images to track the presence and concentration of absorbic acid (AA) as a biomarker of complications in the eye (Misra et al., 2018). The colour transition upon AuNP growth is labelled through an R Hexadecimal value, with a dynamic detection range of 50–2000 μM being reported. Zheng *et al.* recently used a smartphone for quantification of *E. coli* bacteria with the use of 4-mercaptophenylboronic acid functionalized AgNPs (MPBA-AuNPs) (Zheng et al., 2018). The MPBA facilitated aggregation between AgNPs in the absence of bacteria and nanoparticle separation in the presence of *E. coli*. A colour change from yellow to brown was observed and RGB values detected the concentration of E. coli in a range of 5×10^5 cfu/mL–1×10^7 cfu/mL. A recovery rate of

93.4% - 107% were reported within *E. coli*-spiked tap water samples. The ability to employ smartphones in quantification is clearly exemplified but does also have some drawbacks that need to be considered. Specifically, the low sensitivity needs to be addressed while automation of variables such as camera and cuvette location is essential for ensuring that smartphone readout is facile for users around the world. The implementation of a light box is a simple solution for this (Yakoh et al., 2018). Calibration in particular causes issues as both Hexadecimal and RGB values are sensitive to lighting, white balance and phone sensors, making the need for calibration each time important (Amirjani and Fatmehsari, 2018; Russell and de la Rica, 2018).

To combat these challenges, certain properties of the immunoassay can be exploited to eliminate the number of variables that need to be considered in calibration of the images. In order to limit the dependence on light variation, Russell and de la Rica produced a design based on the recognition of a unique pattern printed on a paper transducer (Russell and de la Rica, 2018). When separate, non-aggregated AuNPs are added to paper, the pattern is not recognized by a smartphone-based application due to the intensely colored colloidal suspension, which lessens local contrast and blocks recognition. On the other hand, upon AuNP aggregation, less visible light is absorbed due to the extinction spectrum of AuNPs broadening and dampening. This results in a smaller impact on local contrast and allows the app to recognize the pattern and transmit a message to the user. They were able to establish an LOD of 3×10^{-8} g/mL for the analyte C-reactive protein (CRP) which is on par with the results from competitive ELISA. Their method allowed for the detection of small variations in concentrations otherwise undetectable by the naked eye (Russell and de la Rica, 2018). Essentially, they take advantage of a smartphone's recognition ability rather than use it in colour differentiation, removing many variables associated with lighting, white balance and saturation. Thus, it would be ideal to incorporate consistent smartphone readout with plasmonic colorimetric detection POC testing.

4.2.3. Multiplexing

There has been continued research into various ways to make colorimetric multiplex a possible method to pursue the specificity of DNA sequences. An example of this is multiplexing through the use of target-specific linkers. Zagorovsky *et al.* employed a DNAzyme for the detection of 4 different pathogen biomarkers (Zagorovsky and Chan, 2013) (Fig. 3A). Being held together by specific linkers, AuNPs began in an aggregated state. These linkers included a substrate sequence that can be cut or cleaved by the DNAzyme, multicomponent nucleic acid enzyme (MNAzyme). The presence of the target activates MNAzyme allowing it to hybridize to the substrate sequence of the linkers, degrading them and dispersing the AuNPs (Zagorovsky and Chan, 2013). The changing of the DNA-based sensor bridges on the MNAzyme can cause it to be activated by a particular target while also ensuring that it hybridizes to a specific substrate. They were able to simultaneously test for the presence of genetic sequences for gonorrhea, syphilis bacteria, malaria parasite and HBV. A sensitivity of 50 pM for each biomarker was reported simultaneously. Alternatively, by applying a silver nanostructure, multiplexing was also made possible and distinctive. Han et al. were able to use and manipulate hierarchically branched silver nanostructures (HBAgNSs) for the detection of DNA target sequences related to Ebola, HIV-1 and HBV (Han et al., 2012). Three distinctive plasmonic nanoprobes were used, AgNPrs, AgNPs and AuNPs, and they each resulted in a respective colour shift. These nanoprobes were functionalized with DNA sequences complementary to the target DNA sequences and HBAsNSs surfaces. Upon DNA hybridization to the HBAgNSs, 8 different colour combinations of aggregated structures were created. The LSPR-regulation, surface-functionalization and large surface area-to-volume ratio of HBAgNSs allowed for successful multiplexing (Han et al., 2012). Liu et al. were also able to achieve multiplexing through use of different probes (Liu et al., 2014b). The simultaneous detection of HBV and hepatitis A virus (HVA) was achieved by relating each target analyte (Vall7 polyprotein gene for HVA and HBsAg gene for HBV) to a different nanoparticle, leading to corresponding colours of the solution. Upon colour shift, ranges of 10 - 125 pM for HVA and 25 - 150 pM for HVB were detected. Overall, the different mixture of colours is the best representative way to establish multiplexing within colorimetric assays. This is achieved through relating respective analytes to specific nanoprobes or enzymes, having each colour be represented by a different analyte. Currently, this requires very specific molecular interactions that are usually restricted to DNA hybridization. Continuous research will have to be done as multiplexing can have a huge impact on making POC diagnostics more rapid with a higher throughput.

4.3. Applications of plasmonic colorimetric assay diagnostics

For summary of applications using plasmonic colorimetric assays, see Table 3.

4.3.1. Plasmonic colorimetric platforms for diagnosis of HIV-1

Within HIV-1 studies using plasmonic calorimetric platforms, proteins seem to be the prominent biomarker for detection, leaving capture mechanism along with nanoparticle modification as the two areas with variation that are presented below (Cecchin et al., 2014; de la Rica and Stevens, 2012; Qu et al., 2011; Tang and Li, 2017; Verma et al., 2015). The first method we present is the use of H_2O_2 (Hydrogen Peroxide, HP) to modulate the size of nanoparticles. This method was reported by de la Rica and Stevens, who used this platform for the visible detection of the HIV-1 protein p24 (de la Rica and Stevens, 2012). Detection was achieved through controlling the kinetics of growth of AuNPs in the presence of 2-(*N*-morpholino)ethane-sulfonic acid (MES). MES acts as a weak reducing agent while HP is specifically added to tune the crystal growth kinetics, producing nanoparticles of various morphology and colour transition (Cecchin et al., 2014). An LOD of 1×10^{-18} g/mL was reported upon colour transition. Their design was also successful in the identification of HIV-1-positive clinical samples, even detecting positive samples that could not be diagnosed using the gold standard nucleic acid-based test. Building on this report, Cecchin *et al.* used the same system but for the detection of HIV-1 protein gp120 (Cecchin et al., 2014). Here, an LOD of 8×10^{-20} M was reported. A high sensitivity for both of these platforms is attributed to the ability of the enzyme to effectively, finely tune the concentration of HP and ultimately the colour shift (de la Rica and Stevens, 2012). However, the reproducibility of this method can be questioned as the success of this procedure depends on several factors such as mixing time, equipment precision, age of solutions, reaction scale, impurities in solutions (Cecchin et al., 2014). The stability of HP also has to be considered in the context of POC devices that may have to be stored for longer periods of time. Although the above mentioned challenges still exist for both systems, the ability to distinguish the presence of HIV-1 antigens by eye at a lower level than ELISA (Cecchin et al., 2014) shows great promise going forward for plasmonic colorimetric detectors.

A second modulation method using click chemistry has also been explored. Qu *et al.* utilized Cu^{II}-based click chemistry for the aggregation of AuNPs functionalized with azide and alkyne groups in the presence of HIV-1 protein gp41 (Qu et al., 2011). This copper-catalyzed reaction results in high sensitivity and selectivity as blank samples and unrelated protein control samples did not experience a change in colour. The lowest concentration detected with a visible colour shift was roughly 150 ng/mL. This method also withstood clinical trials, correctly detecting 3 HIV-positive samples. As mentioned in this section, mechanisms can vary greatly in how the nanoparticles are modulated, making it very important that the capture mechanism for HIV-1 detection is dependable in order to detect antigens at a sensitivity applicable for early disease diagnostics.

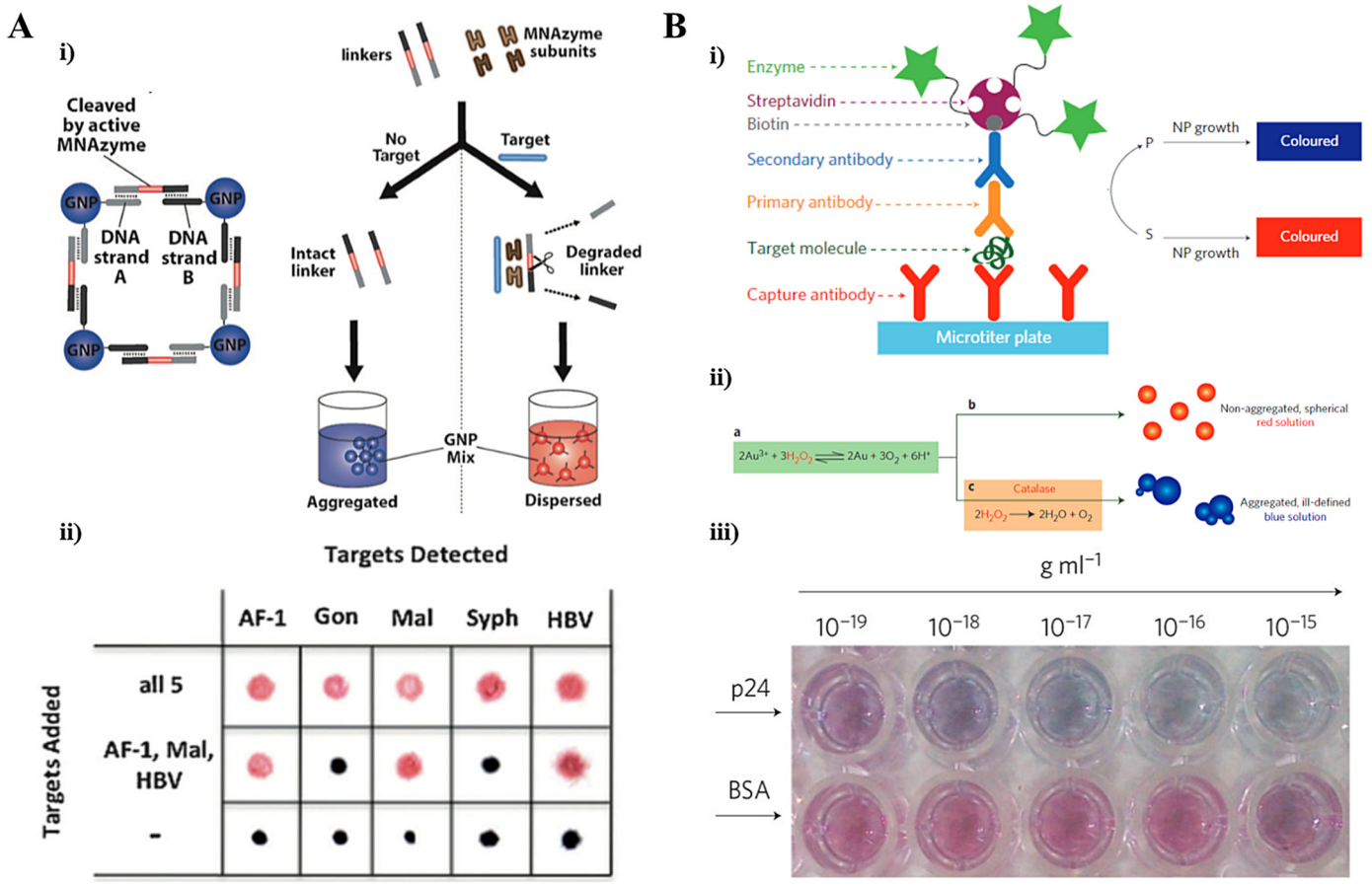


Fig. 3. Mechanism of plasmonic-based colorimetric detection.
(A) Colour transition due to aggregation of plasmonic nanoparticles via MNAzyme (i) MNAzyme cleaves linkers that hold together aggregated AuNPs. (ii) Solution color shifts in the presence of various DNA targets. Adapted with permission from Zagorovsky and Chan, 2013, Copyright 2013 John Wiley and Sons. (B) Plasmonic ELISA for aggregation of plasmonic nanoparticles causing colour shift: (i) Structure of sandwich plasmonic ELISA relating target antigen to concentration of catalase (enzyme) for change in NP size. (ii) Mechanism used for colour transition through reduction of AuNPs by H_2O_2 depending on presence of catalase. (iii) Resulting blue colour transitions depending on concentration of HIV-1 protein p24. Reprinted with permission from de la Rica and Stevens (2012), Copyright 2012 Springer Nature.

4.3.2. Plasmonic colorimetric platforms for diagnosis of Hepatitis B

Recently, efforts have been made to detect HBV biomarkers at low concentrations. Peng *et al.* developed a colorimetric assay through the principle of AuNP growth for the detection of hepatitis B surface antigen (HBsAg) (Peng et al., 2015) (Fig. 3B). In the presence of HBsAg, alcohol dehydrogenase (ADH) catalyzed the reaction between ethanol and NAD^+, producing NADH which is capable of reducing $HAuCl_4$, leading to the enlargement of AuNP seeds (Peng et al., 2015; Verma et al., 2015). The change in size resulted in a visible colour shift, exemplifying an LOD of 1×10^{-12} g/mL when testing concentrations of HBsAg in PBS. To take it further, 4 samples from patients diagnosed with hepatitis B virus demonstrated a colour shift while 4 HBsAg-negative clinical samples did not. HBsAg presence was confirmed through comparison with conventional ELISA and chemiluminescence microparticle immunoassays, which presented the same result, demonstrating that this approach has potential to be used in real sample detection. Exploring other possible biomarkers for HBV may result in novel designs that can benefit from new tools and this flexibility is highlighted by proof-of-concept designs for HBV detection.

In some cases, HBV was used to test the proof-of-concept of designs rather than being the main focus, but this still illustrates the potential for assays to employ different detection strategies for the disease. For example, with the goal of multiplexing, Liu *et al.* produced a colorimetric plasmonic sensing for hepatitis B virus and hepatitis A virus simultaneously. Reporter probes were bound to the surface of AgNPs and were sensitive to the oligonucleotides associated with the HBsAg gene, which was the biomarker for this study (Liu et al., 2014b). Through the use of magnetic beads, AuNPs, which were used to label the presence of HBV, were separated from the solution, changing the colour from orange to yellow, indicating the presence of HBsAg. A detection limit of 15 pM for HBV was recorded. Another example of proof-of-concept testing was given by colorimetric detection of point mutations. Liu et al. were able to detect HBV DNA as well as a single-base mismatch between genes rtM204M and its point mutation, rtM204V (Liu et al., 2011). The goal of their project was to be able to have a colorimetric detection of HBV resistance to anti-HBV drugs rather than just their prescence. They were able to detect a colour shift with the use of real clinical samples, and although it took multiple cycles of PCR to be able to generate a signal, their S1 nuclease-based AuNP aggregation system can still be used as a reference when going forward with colorimetric DNA detection methods. These proof-of-concept designs demonstrate that it is feasible to develop sensitive, specific DNA-based HBV detection POC testing with potential multiplexing capability.

4.3.3. Plasmonic colorimetric platforms for diagnosis of Tuberculosis

For the colorimetric detection of Tuberculosis, DNA was employed, allowing sensitive detection of TB DNA down to the nM level. Tsai *et al.* were able to design a label-free, paper-based device for the diagnosis of TB by employing the hybridization of targeted TB DNA with single-stranded DNA probe molecules (Tsai et al., 2017). This hybridization resulted in a change in surface charge density of combined AuNPs, which ultimately led to their aggregation. An LOD of 1.95×10^{-2} ng/

Table 3
Summary of plasmonic colorimetric diagnostics for various infectious diseases.

Disease	Type of biomarker	Biomarker	Biorecognition capture	LOD	Sample for detection	Notes	Reference
HIV-1	Protein	Protein gp120	Anti-gp120	8×10^{-20} M	FBS		Cecchin et al. (2014)
HIV-1	Protein	Protein p24	Anti-p24	1×10^{-18} g/mL	Whole serum		de la Rica and Stevens, (2012)
HIV-1	Protein	Protein gp41	Anti-gp41	150 ng/mL	Rabbit serum		Qu et al. (2011)
HBV	Protein	HBsAg	Goat IgG	1×10^{-12} g/mL	PBS	Used ADH-labelled secondary antibody for signal amplification	Peng et al. (2015)
HBV	Nucleic Acid	HBsAg gene	Oligonucleotide capture probe	15 pM	PBS-T	Employed use of non-negative matrix factorization for spectrum analysis	Liu et al. (2014b)
HBV	Nucleic Acid	Gene rtM204M	Structure-selective nucleases (S1, DNS)	N/A	Buffer solution	Method designed for point mutation detection	Liu et al. (2011b)
TB	Nucleic Acid	IS6110 DNA sequence	Single stranded detection oligonucleotides	1.95×10^{-2} ng/mL	Buffer solution	Use of paper-based device and smartphone read-out	Tsai et al. (2017)
TB	Nucleic Acid	IS6110 DNA sequence	Single stranded detection oligonucleotides	2.6 nM	Tris-borate buffer	Use of paper-based device and smartphone read-out	Tsai et al. (2013)
TB	Nucleic Acid	*gyrB* gene sequence	Thiol-linked oligonucleotide-modified AuNPs	N/A	Phosphate buffer	Method used to distinguish between members of MTC	Costa et al. (2010)

mL and a dynamic range of 1.95×10^{-2}–1.95×10^{1} were reported and were able to be quantified through the use of a smartphone. Feasibility of this device was further confirmed through the positive detection of the DNA within a sample from a TB-positive patient. Earlier, Tsai et al. followed this same technique for the presence of TB DNA but incorporated it into a microfluidic paper-based analytical device (Tsai et al., 2013). Single-stranded DNA prevented the aggregation of AuNPs by NaCl in the absence of target DNA, but upon hybridization of the ssDNA with the TB DNA, aggregation of the AuNPs resulted in a colour change. 2.6 nM of MTBC target sequences could be detected through the use of a smartphone once again. The turnaround time for this protocol is reported to possibly take no more than 1 h. DNA sequences as specific targets were also exemplified in Costa et al.'s design. Their device can differentiate between members of the *Mycobacterium tuberculosis* complex, including *M. tuberculosis* and *M. bovis* (Costa et al., 2010). This was achieved through the development of different Au-nanoprobes for each respective target. Aggregation was caused by the use of thiol-linked ssDNA-modified gold nanoparticles in the presence of salt, and then the absence of target DNA results in aggregation and vice-versa. Although no LOD was specified, this method shows that the detection and differentiation of TB and closely-related species is very much possible through the use of specific DNA sequences. Plasmonic colorimetric devices are still in development and although current devices consider nucleic acid as the preferred biomarker, it is very possible that other biomarkers such as lipoarabinomannan will be considered in the future.

5. Surface enhanced Raman spectroscopy (SERS)

5.1. Principles of SERS

Surface-enhanced Raman spectroscopy (SERS) is another leading candidate in the detection of biomarkers as it takes advantage of plasmonic properties to be able to fully utilize the abilities of Raman spectroscopy. Raman spectroscopy studies the vibrational and rotational modes of analyte molecules through the analysis of inelastic (Raman) scattering of monochromatic light. The incident photons interact with the vibrational and rotational motions of a molecule, resulting in either a loss or gain in energy of these incident photons. This shift in energy is specific to the molecular structure and produces a Raman spectrum that acts as a structural fingerprint unique to the individual molecule. The potential to distinguish molecules based on their spectroscopic "fingerprint" can be very valuable and is employed in various biological applications. However, Raman scattering is a scarce occurrence, as approximately only 1 in 10^6–10^{10} photons are scattered inelastically (Zhang et al., 2011). This results in a low scattering cross-section and ultimately weak signal intensities, leading researchers to strive for novel methods to overcome these challenges. It has been shown that Raman scattering signals can be enhanced by factors of 10^4–10^8 when the analyte molecule is near or at a rough noble metal surface (Fleischmann et al., 1974; Jeanmaire and Duyne, 1977). This phenomenon is known as SERS and it has been applied to diminish the disadvantages of normal Raman spectroscopy, allowing it to further play an important role in disease diagnostics.

SERS is thus the result of a plasmonic phenomenon that can result in an extensive increase in the intensity of the inelastically scattered light needed to produce a Raman spectrum. As mentioned previously, this phenomenon occurs when the analyte molecule is absorbed onto metal films with roughened surfaces or nanoscale patterns (Fleischmann et al., 1974; Jeanmaire and Duyne, 1977). This enhancement effect is attributed to two different mechanisms, an electromagnetic effect (EME) and a chemical effect (CE). The EME is dependent on the effect of localized surface plasmon resonance (LSPR, as described in Section 3). The excitement of localized surface plasmons with the use of light causes an oscillating polarity of the incident field (Kelly et al., 2003). Due to this, the particle emits its own dipole field, which enhances the

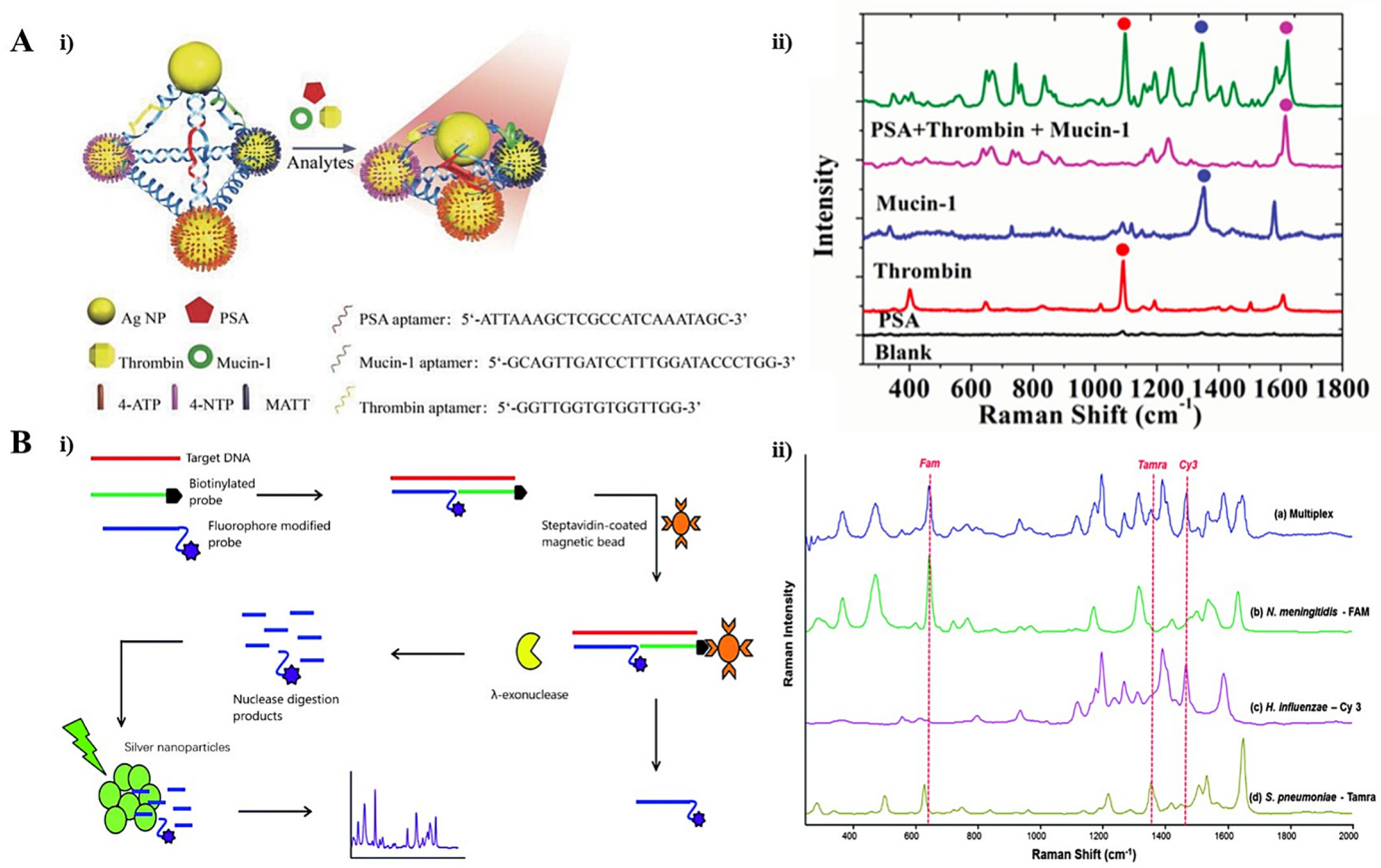


Fig. 4. Multiplexing options for SERS detection platforms.
(A) Self-assembled nanopyramids for multiplexing: (i) Silver nanoparticle pyramid with DNA frame containing biomarker specific DNA aptamers and labels. (ii) Contraction of DNA frame due to multiplex binding of analytes results in SERS spectrum with three peaks. Adapted with permission from Xu et al., 2015, Copyright 2015 John Wiley and Sons. (B) λ-Exonuclease-mediated multiplex detection of DNA targets: (i) DNA target (red) is simultaneously hybridized to a 3' biotinylated probe (green) as well as a 5'-phosphate modified probe possessing a 3' fluorophore (blue). Streptavidin coated magnetic beads (orange) allow for isolation of hybridized target. λ-exonuclease (yellow) digested products are added to a AgNPs (green sphere) solution for SERS analysis. (ii) SERS spectra of multiplex and individual pathogens with the red-dotted line depicting unique peaks of label (*i.e.,* Tamra, Cy3, FAM). Adapted with permission from Gracie et al., 2014, material reproduced under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0.

electromagnetic field on the surface of the particle. Raman scattering is dependent on the dipole moment of the molecule, which in turn is dependent on the electric field strength being applied (Stuart et al., 2005). Therefore, this increase in electric field strength leads to enhancement factors of 10^2–10^4 when the molecule is near the roughened metal surface (Zhang et al, 2011). The CE is described as the chemisorption of the analyte molecule to the surface of the metal film. This causes a charge transfer between the molecule and the metal surface, meaning the electrons of the molecule are now able to interact with the electrons of the metal surface (Otto, 1991). These interactions can result in enhancement factors of between 10^2 and 10^3 (Lane et al., 2015). The metal films that are used in the application of SERS are mainly composed of gold or silver with varying thicknesses of 10–200 nm (Haes et al., 2005). Improved ease-of-use and speed over competing assays such as ELISA and fluorescent probes presents SERS as one of the leading contenders for POC diagnostics (Granger et al., 2016).

5.2. Recent advancements in SERS biosensors

5.2.1. Substrate fabrication

Quick, easy and reproducible methods to produce enhancing and stable SERS substrates are now a large area of focus for researchers and have resulted in the development of many new designs (Fu et al., 2016; Granger et al., 2016; Lane et al., 2015; Sakir et al., 2017; Xu et al., 2015; Zhang et al., 2018). Kaminska et al. produced a porous silicone (PS) surface that was coated by a thin gold layer in a simple two-step method for stable SERS activity (Kamińska et al., 2018). The PS nanostructure was prepared by galvanostatic anodic etch of crystalline silicon wafers with a gold coating being placed on top through sputtering. The resulting SERS device produced an enhancement factor of 1×10^8. The morphology of the Au-coated PS was consistent with the ideal size of nanostructures for LSPR resonance (50–70 nm) (Kamińska et al., 2018). This was a scalable procedure that maintains a non-expensive and facile method of production. Other simple methods are proposed that require even less complex machinery. One example of this is Xu *et al.*'s quick and facile production of their substrate through uniaxial stretching of a flexible poly (ε-caprolactone) (PCL) SPR film with an Ag film deposited on top. The uniaxial stretching produced a substrate with nanogrooves throughout the brittle Ag film, leading to the formation of LSPR hotspots for increased signal amplification (Xu et al., 2017). A flexible, transparent SERS substrate was produced without the need for complicated lithographical processes. Thermal stability was also shown as there was almost no degradation of its Raman signals even when performed at a temperature of 323 K. Further investigation regarding the functionalization of the substrates mentioned above is also vital to producing devices with enhanced specificity while still being able to maintain stability. AuNPs tend to have better biocompatibility, can be functionalized with relative ease and were easily implemented into Liu et al's substrate design. Liu et al. designed a plasmonic paper device for a sensitive, non-invasive sensor

Table 4
Summary of SERS diagnostics for various infectious diseases.

Disease	Type of biomarker	Biomarker	Biorecognition element	LOD	Sample for detection	Notes	Reference
HIV-1	Nucleic acid	HIV-1 DNA sequence	Oligonucleotide detection probe-conjugated AuNPs	0.24 pg/mL	SSC buffer containing 1% BSA	Sensor developed in an LF system	Fu et al. (2016)
HIV-1	Nucleic acid	HIV-1 gag-gene sequence	Oligonucleotide detection probe	N/A	N/A	Hybrid graphene oxide nanopopcorn used for large enhancement factor	Fan et al. (2013)
HIV-1	Virus-like particles	HIV-1 virus-like particles	Anti-gp120	35 fg/mL	DMEM		Lee et al. (2015)
HBV	Amino acid	L-arginine, phenylalanine, tyrosine	N/A	N/A	Human blood serum	Use of PCA for spectrum analysis to diagnose HBV	Lu et al. (2018)
HBV	Protein	HBsAg	Anti-HBsAg	4.3 fg/mL	Human blood plasma	Implemented with a microfluidic device	Kamińska et al. (2015)
TB	Glycolipid	ManLAM	Anti-ManLAM	2 ng/mL	Human blood serum		Crawford et al. (2017)
TB	Raman-active molecules	N/A	N/A	N/A	Human blood serum	Multivariate statistical methods used to diagnose TB	Botta et al. (2018)
TB	Fatty acid	Mycolic acid	N/A	N/A	Tris EDTA buffer	Multivariate statistical methods used to diagnose TB	Mühlig et al. (2016)

(Liu et al., 2014a). The cellulose-based filter paper was submerged in a solution containing CTAB-capped gold nanorods (AuNRs) for 24 h and the AuNRs adsorbed due to their positive charge bearing attraction to the negatively charged filter paper, exemplifying a very facile production process (Liu et al., 2014a). This paper-based SERS sensor is easy-to-manufacture, cheap, rapid, flexible, stable and portable (Granger et al., 2016). There are a variety of ways to produce a SERS substrate with the necessary shape and spacing of Au or Ag nanoparticles in facile and simplistic ways, and with the end goal of simplistic methods to modulate these substrates in mind, novel fabrication methods can continue to arise in the near future.

5.2.2. *Multiplexing*

The driving force of SERS multiplexing is the association of different biomarkers with a respective label and capturing it onto a SERS-active substrate. For instance, Xu *et al.* prepared a DNA-frame driven silver pyramid (Ag-pyramid) for detection of multiple biomarkers simultaneously (Fig. 4A). Prostate specific antigen (PSA), thrombin and mucin-1 were targeted (Xu et al., 2015). Their pyramid was developed using 4 AgNPs bound to specific Raman labels used to determine the presence of a specific biomarker. The pyramid contained a "DNA-frame" which would contract upon presence of any of the analytes. This reduces the gap between the AgNPs, forming more hotspots and amplifying the SERS signal in the presence of biomarkers. Multiplexing was possible by coating each of the AgNPs with a different Raman label and including 3 different aptamers for each respective biomarker within the DNA-frame. Neng *et al.* also developed a multiplexing platform but with use of AuNPs and paramagnetic nanoparticles (PMPs) (Neng et al., 2013). They were able to simultaneously detect West Nile virus envelope E protein and Rift Valley Fever virus nucleocapsid N protein. The AuNPs were coated with Raman reporter molecules as well as corresponding antibodies to the particular virus protein. The PMPs also contained a capture antibody creating an immunoassay complex that was positioned within the hotspots of the aggregated AuNPs (Neng et al., 2013). Multiplexing was possible by differing the capture antibody as well as the Raman label to be specified for each of the two biomarkers. These are two examples of simultaneous capture mechanisms embedded in the same system.

A more distinct type of biomarker that has high potential for multiplexing capabilities is the use of nucleic acid detection, which entitles high specificity. Zhao *et al.* created SERS-active nanogap-gold nanostructures, termed polyA non-fluorescent nanotags (pA-nF-NTs) (Zhao et al., 2014). Five types of pA-nF-NTs were synthesized and functionalized with different Raman reporters as well as capture probes for multiplexing abilities. To prove multiplexing abilities, they had their design analyze the presence of hepatitis A virus (HAV), HBV and HIV-1 DNA markers. Their design proved successful as the number of Raman peaks observed corresponded to the number of types of DNA in the sample. They further proved the ability of their nanotag to be used in conjunction with other types of probes. MiRNa-141 (miRNA), platelet-derived growth factor (protein) and cocaine (small drug molecule) were selected as target molecules. Specific probe DNA, aptamer and engineered aptamer were functionalized onto the surface on the nanotags accordingly. Similarly, three distinct Raman peaks were visible corresponding to each appropriate Raman label, thus exemplifying the versatility of this SERS-active nanostructure. In a different method, Gracie *et al.* created a SERS-based device capable of quantificating three different bacterial meningitis pathogens but through the use of spectrum analysis rather than differential labelling (Gracie et al., 2014). This was achieved through the detection of the respective DNA sequences of the bacterial strands that hybridize with subsequent DNA probes containing a fluorphore modification (Fig. 4B). λ-Exonuclease was then used to digest the 5'-phosphate modified probe, releasing a fluorescent dye label which was then mixed into a solution containing silver nanoparticles (AgNPs) used to conduct SERS analysis. *N. meningitidis*, *S. pneumonie*, and *H. influenza* were detected simultaneously. Each target

was associated with a respective dye and SERS spectra were obtained from the solution. These spectra were further inspected with the help of principal components analysis (PCA), and all three bacterial pathogens were simultaneously in the same mixture. PCA is a statistic-based method that can be used to distinguish specific peaks from a complex vibrational pattern in order to identify specific molecules (Alvarez-Puebla and Liz-Marzán, 2010). This level of multiplexing is very encouraging to go forward while proving that PCA is essential for SERS diagnostics. The use of DNA and its specificity clearly plays a key role in multiplexing and most likely continues to be used in the future design.

5.3. Applications of SERS diagnostics

For summary of applications using SERS modalities, see Table 4.

5.3.1. SERS platforms for diagnosis of HIV-1

A commonly employed method for SERS detection of HIV-1 is through the use of DNA sequences specific to the virus. Fan *et al.* were able to improve on the specificity and reproducibility of an HIV-1 SERS-based sensor through the use of a graphene oxide base with popcorn AuNPs attached to the surface (Fan et al., 2013). The HIV-1 *gag* gene was used as the target DNA. The hybrid SERS probe detected the characteristic Raman peaks of HIV-1 DNA on the femto-molar level (500 fM) upon capture by DNA probes. This is attributed to the ability to adjust both the chemical and electromagnetic enhancement effects using this substrate. 6 different spectra were also recorded, all nearly identical, showcasing the reproducibility of this design's results. While this proof-of-concept design demonstrates that SERS can be used in the detection of HIV-1 target DNA sequences, it leaves much to be desired moving forward regarding potential use of the platform in POC devices, as sensitivity, portability and reproducibility, among other properties, have to be better represented.

To combat this, SERS technology can be infused with other POC technologies currently in use. Fu *et al.* designed a SERS-based lateral flow (LF) strip biosensor system (Fu et al., 2016). They similarly used a specific DNA sequence of the virus as a method of hybridization or capture. The system was based on a sandwich assay described as "DNA-conjugated AuNPs-target DNA-capture DNA" (Fu et al., 2016). The AuNPs used in this experiment were functionalized with a Raman reporter and detection oligonucleotides. These AuNPs were then placed on the conjugate pad of the LF strip. As the buffer solution containing the target DNA migrated along the strip, the sandwich assay described above was produced. A red line at the test line was then visible to the naked eye or detected at lower concentrations by employing SERS. Through this method, an LOD of ~0.24 pg/mL was reported using SERS. Their SERS-based assay was compared with a commercial HIV-1 assay kit with the SERS-based assay presenting a detection level 10 times lower than that of the kit (Fu et al., 2016). The combination of SERS and LF technologies has produced a design more suited for POC diagnostics while creating a pathway for more sensitive detection. However, the noticable drawback when using a complimentary DNA sequence is that SERS spectra were affected when in the presence of a non-complimentary DNA sequence (Fan et al., 2013; Wabuyele and Vo-Dinh, 2005). This may cause further problems when going forward with clinical sample detection that is necessary for a POC-ready design. In clnically relevant samples such as serum, saliva or semen, the presence of non-complimentary sequences is greatly enhanced, possibly causing further non-specific binding that may lead to inconclusive results.

Few other biomarkers have been reported in SERS use, prompting the exploration of creating a custom biomarker. Instead of using DNA, Lee *et al.* used antibodies to capture HIV-1 virus-like particles (VLPs) on an indium tin oxide (ITO) substrate covered in Au nanodots (Lee et al., 2015). The HIV-1 VLPs consisted of co-transfected HEK293 cells containing the Gag, Pol and Env genes of the HIV-1 virus. Surface-bound antibodies were used to capture the VLPs, leading to concentrations in the range of 35 fg/mL–350 pg/mL being detected. Upon review of their feasibility, the production of the virus-like particles may be significant in SERS detection of HIV-1 going forward. Exploring new HIV-1 biomarkers may help improve specificity in HIV-1 SERS-based detection devices, which would take another step forward in the creation of an applicable POC device by removing the need for preprocessing steps of the sample (Kamińska et al., 2015; Ngo et al., 2013; Zhang et al., 2018).

5.3.2. SERS platforms for diagnosis of Hepatitis B

SERS platforms have also been used to detect HBV in a quick and simple manner. For instance, Lu *et al.* used a standard, label-free Ag nanoparticle solution as the SERS-active substrate to test blood serum samples from HBV patients and healthy volunteers (Lu et al., 2018). Instead of testing for a specific biomarker, data analysis tools were used in conjunction, with PCA alongside linear discriminant analysis (PCA-LDA) being used to compose a diagnostic algorithm. The SERS spectra of the serum samples from both the infected patients and healthy volunteers were compared following this algorithm. Using this approach, a spectrum was produced in 10 min for each sample with a diagnostic sensitivity of 91.4% when using the derivative SERS spectrum. This shows great potential for a quick, non-invasive, label free diagnostic method through the implementation of PCA.

SERS substrates can produce a higher enhancement factor not only through the use of new materials but also combinations of known ones. Kaminska *et al.* produced a SERS-based sensor using a GaN substrate covered with Au-Ag and employed the use of a Raman label consisting of Au nanoflowers (Kamińska et al., 2015). This created a sandwich assay with HBV antigen (HBsAg) as the biomarker being detected. The GaN substrate allows generation of an enhanced electromagnetic field around the Au and Ag nanoparticles as well as the substrate. It is reported that this leads to larger enhancement factors as well as high stability (Kamińska et al., 2015). Dilutions of HBsAg were tested in a range from 0 to 625 IU/mL, with the LOD estimated to be 0.01 IU/mL. The produced assay gave precise results over a broad range as well (0.0125–60 IU/mL). These results are comparable to clinically relevant concentrations of HBsAg (0.125–25 IU/mL) (Kamińska et al., 2015). The SERS spectrum was quick (10 min) but other sample preparations need to be taken into consideration. Extraction of blood plasma required 15 min, which decreases ease of use when considering POC applications. The application of statistical methods such as PCA-LDA could be further researched to possibly accommodate the use of whole samples in this platform.

Alternatively, nanopatterned substrates can be used instead to increase signal amplification. Yao *et al.* produced an Au nano-structured surface substrate consisting of high-density triangular cavities for sensitive HBV detection (Yao et al., 2012). The capture of HBV was conducted with respective antibodies while Coomassie Brilliant Blue dye was introduced to the assay, allowing levels of 10^{-10} M to be discernable for HBsAg, the chosen HBV biomarker. Li et. al also produced a nanopatterned sensor, but one which was capable of ultra-sensitive detection as low as 50 aM (Li et al., 2013). They achieved this through a sandwich assay consisting of an Au triangle nanoarray substrate and an Ag nanorice structure containing a Raman label covered by an SiO_2 shell. They took advantage of the pairing of colloids with a periodic nanoarray to increase the LSPR field and raise the EM enhancement factor through this method. They used HBV DNA as a target and used single-base mutants of the DNA to successfully test specificity of the sensor. As mentioned, an LOD of 50 aM was determined, the lowest of any sensor reported in the literature (Li et al., 2013). The ability of engineered nanosubstrates can be applied to further expose the EM effect and increase enhancement factors for SERS sensors. It is now a matter of being able to manufacture these substrates with high repeatability and at a suitable cost as the fabrication can be complex and lack reproducible enhancement factors (Bantz et al., 2011).

5.3.3. SERS platforms for diagnosis of Tuberculosis

Due to current challenges and landscape mentioned for TB

diagnostics, developing methods for early TB biomarkers is imperative and has been investigated using SERS approaches. For example, Crawford *et al.* developed sandwich assay to capture mannose-capped lipoarabinomannan (ManLAM), a TB biomarker, for SERS detection using AuNPs as the SERS-active substrate (Crawford et al., 2017). ManLAM was captured with the use of ManLAM monoclonal antibodies and after a sample pretreatment step (acidification) was performed on the serum used, extrinsic raman labels were bound to the biomarker using a linker to form the immunoassay. Upon SERS analysis of the assay, the LOD was reported to be 2 ng/mL. When the device was applied to test 24 TB-positive and 10 TB-negative samples, TB was accurately detected in 21 of the 24 samples, while all 10 healthy controlled samples were shown as negative. While this does validate the potential value of the application of this device in the detection of TB, it is noted that other body fluids are difficult to use as samples due to low concentrations of unbound antigen. Alternatively, through the use of sample spectra analysis, Botta et. al was recently able to successfully detect and differentiate the presence of tuberculosis within healthy and infected samples through the use of 4 novel silver nanostructures as SERS substrates, with vertical nanorods displaying the highest intensity (Botta et al., 2018). Along with the assistance of chemometric methods such as PCA, SERS spectra of patient serums were collected and analyzed, leading to clear distinguishing attributes between the two groups. However, only 2 samples were used, meaning there is insufficient data to truly understand if this method is viable. Building on this, Mühlig et al. were also able to detect *Mycobacteria tuberculosis* complex (MTC) species by implementing SERS with a lab-on-a-chip (LOC) design (Mühlig et al., 2016). Their LOC-SERS device was made for a safe, fast, and reproducible method to disrupt mycobacteria using a bead-beating module, allowing a SERS spectrum to be obtained of mycolic acid, a cell-wall component. The disrupted bacterial suspension was flown onto a SERS substrate of AgNPs where a SERS spectrum of the sample was recorded. Upon data analysis of various spectra using PCA, MTC species were identified with 100% accuracy. This again illustrates the ability of PCA to be of great assistance in distinguishing the necessary components of a Raman spectrum needed for the diagnosis of a disease. Producing an efficient and accurate method of pathogen detection using just the SERS spectrum of a biological sample would be a solution to eliminating the need for sample preparation, allowing these devices to be more reliable for POC diagnostics and deployable to the low-resource areas that can fully benifit from their advancements.

6. Microfluidic integration

Over the past two decades, rapid development in the field of microfluidics has brought on a new generation of POC diagnostic devices within the healthcare landscape. Geometric constraining of fluids within networks of channels provide microfluidic devices with advantageous properties such as high surface area-to-volume ratios, inexpensive fabrication, precise control, adaptability and quick results, as well as mimicking physiological and cellular environment. Compared with current gold standard tests for pathogen detection and quantification techniques, microfluidic-based diagnostic technologies hold certain advantages, including lower turnaround time, and higher portability, efficiency and automation (Chin et al., 2012). The realization of diagnostics in microfluidic systems has already been highlighted for the detection of bacteria and virus such as *E. coli,* TB, HIV-1 rapidly from complex biological media (Demirci et al., 2012; Mani et al., 2016; Wang et al., 2012). Integrating plasmonic technologies into microfluidic platforms can further enhance the sensitivity of current microchip assays while taking advantage of both plasmonic and microfluidic properties for feasible POC deployment and commercialization.

Following these trends, many recent plasmonic LOC platforms outperform gold standard tests in the sensitivity, portability and multiplexing capabilities while leveraging the advantageous LOC properties. For instance, (Inci et al., 2015b) developed a 3D LSPR surface sensing scheme for enhanced electric field amplification of the surface AuNP layer. This design was implemented in both a standard 96-well plate reader format and disposable microfluidic chip. No statistical differences were observed between the two, validating the potential for its use as a portable platform. The highlights of this platform have exciting implications for POC deployment of plasmonic-based platforms, such as low per test costs ($1.25 USD compared to $200–600 USD for gold standard ELISA of NAATs), multiplexing of various biomarker types (i.e. proteins, drugs, whole viruses and whole bacteria), high sensitivity (400 fg/mL), stability in inconsistent environmental conditions such as temperature, repeatable (91%) readouts, and low sample volume used in unprocessed biological fluids (whole blood, serum and simulated saliva). With further optimization and miniaturization of hardware componenets such as light source, detector or pump, and hybridization with smartphone all-in-one platforms, the utility of multiplexable LOC devices can be leveraged to address the recent global health crises of HIV-1 and TB co-infection.

Moreover, the limitations of nucleic acid detection methods within POC frameworks lie in extraction and amplification which need significant preprocessing steps. Circumventing this problem is important to fully realize the potential of the high sensitivity and specificity of nucleic targets in early diagnosis. Leveraging microfluidics, Nguyen et al. have developed a microfluidic SPR platform with inline PCR in lieu of this problem ((Nguyen et al., 2017). Although an LOD was not specified, this platform investigated the minimum amplification cycles (15) within the device in order to obtain a readable optical fiber SPR signal. Furthermore, LAMP methods mentioned previously have also been employed on LOCs showing increased sensitivity and portability (Chen et al., 2017; Damhorst et al., 2015). With smartphone readouts and signal analysis using plasmonic-based biosensors employed on these platforms, the elimination for fluorescent labels or benchtop equipment can also improve scalability. Further improvements can be made for better POC feasibility, such as further miniaturization, improvement of device regeneration after each sample and elimination of preliminary processing steps as the problem of DNA extraction is not addressed.

Advances in microfluidics are intertwined with improvements for POC-applicable designs, providing solutions for common plasmonic sensor issues such as sample preparation and platform stability. Since plasma is often used for testing proof-of-concept sensors as the clinical medium, providing a quick way to simplify this extraction process for end users is critical for POC applications. Specifically, the separation of plasma from whole blood samples can be achieved in a confined, controlled and timely manner through microfluidic integration. For example, a microchip was designed to extract plasma from whole blood with 98% purity in a timespan of under 5 min without the use of any external forces (Madadi et al., 2015). Separation efficiency was enhanced through the coating of a polydimethylsiloxane device with a surfactant, resulting in a hydrophilic nature that is used to delay filtration clogging caused by red blood cells, maximizing extracted plasma. Their device was also integrated with lateral flow immunochromatography technology, demonstrating the ability to implement these devices with corresponding plasmonic immunoassays. Another extraction process that can benefit from microfluidic integration is the isolation of DNA from clinical samples. The use of nucleic acids can help improve the sensitivity and specificity of a plasmonic sensor and so being able to automate the extraction process can help achieve a more field-ready design. Oblath *et al.* were able to extract DNA from saliva samples using their microfluidic device (Oblath et al., 2013). A monolithic aluminum oxide membrane (AOM) was used to extract and concentrate DNA from the saliva sample after heating to lyse the cells. The step took a few minutes and captured sufficient gDNA to detect 100–125 copies of spiked bacteria in the whole saliva sample. Microfluidics present a platform in which AOMs can easily be implemented and provide a reliable, onestep process that is integrated into the sensor design, holding a large promise for future POC applications. They also

present a way to enhance chemical stability. Within plasmonic sensors, multi-layer immune-functionalization results in preferred orientation for antibodies, leading to increased capture efficiency and more effective devices. However, low temperatures are needed to ensure that antibodies are not denatured, complicating transportation and storage methods. In response, Asghar et al. created biologically active surfaces for longer shelf-life in microfluidic devices (Asghar et al., 2016). Specifically, trehalose was employed for the refrigeration-free preservation of multi-layer functionalized microfluidic surfaces. An assay built for CD4 T-cell counting remained effective for up to 6 months of storage at room temperature. Along with stability over time, this method displayed thermal and humid stability as well. After heating to 50°C, capture efficiency remained at 79.5% while efficiency was at 74.6% when the device was used after exposure to 85% humidity (Asghar et al., 2016). Aside from presenting a portable, facile option for POC-based plasmonic sensors, microfluidics are also a path to integrate new solutions for roadblocks that are obstructing the application of plasmonic biosensors at the POC.

7. Conclusion and future outlook

The recent advancements in the field of plasmonic biosensors over the past few years have been encouraging. The potential held within the favourable optical, physical and chemical properties of nanostructures has been realized and continues to be developed. This continuous effort has allowed us to produce plasmonic devices capable of overcoming challenges associated with current diagnostic techniques such as ELISA, PCR, fluorescence and nucleic acid tests (Brolo, 2012; D. Howes et al., 2014; Granger et al., 2016; Mejía-Salazar and Oliveira, 2018; Satija et al., 2016; Spackova et al., 2016; Zhou et al., 2015). Sensitivity, simplicity and speed are all major benefits that plasmonic-based platforms can offer compared to traditional gold standard methods. A focus on nanofabrication, surface functionalization, cost reduction and miniaturization have also led to more effective plasmonic biosensor designs. Despite this and the many advancements over the past decade, there are still many obstacles limiting POC application, and as such, development will continue to address these lagging aspects.

The ASSURED framework for POC devices proposed by the WHO is an excellent template to follow when researchers are considering their designs, but these goals are often quite challenging to ahieve, with plasmonic devices being no exception. Arguably, the greatest concern is that plasmonic substrates can suffer from decreased specificity due to the use of complex clinical samples. This has ultimately limited the progress of plasmonic biosensors as many are limited to testing samples within buffer solution or preprocessed samples rather than whole clinical samples. In resource-limited areas where these preprocessing steps may not be readily available, POC devices require the input of whole biological sample (whole human blood, urine, cerebrospinal fluid or saliva) to create a sensor that is deliverable to end users. Although sensitivity is highly enhanced through plasmon resonance, external equipment is often needed to sense either changes in refractive index or the raman spectra. This is an impedance to both affordability and ease of use which can be solved through colorimetric methods, but this is usually at the expense of lowering sensitivity. Producing methods of consistent and quick device fabrication also stands as an important factor when considering widespread, affordable availability of these devices. A large amount of plasmonic substrates implement nanoscale designs on their surface to induce a greater enhancement factor, but this might be at the cost of reproducibility. All three of these challenges need to be confronted while also constantly improving sensitivity, speed, portability, stability and price as researchers work towards the goal of commercial, clinically relevant sensors through the guidance of the ASSURED principle (Brolo, 2012; Mejía-Salazar and Oliveira, 2018).

Interestingly, the future of plasmonic-based biosensors and solutions to their problems can be tethered with the advancements realized in other fields of science and technology. For example, over the past decade, the principles of nanofabrication have become more understoodable and established. This has allowed the production of plasmonic substrates to become more consistent and easily accessible, resulting in a wider field of research for plasmonic biosensing (D. Howes et al., 2014). As nanofabrication continues to be improved, we can expect to see more automated and reproducible methods for producing complex nanostructured substrates, used in almost all of the platforms covered in this review, and ultimately an important step in ensuring future commerialization. Furthermore, future progress in the field of surface chemistry can yield more efficient immobilization of antibodies but more importantly, can limit the amount of nonspecific bonding between antibody-antigen complexes (Spackova et al., 2016). New areas such as quantum plasmonics can also start seeing a larger focus as the field of quantum mechanics is constantly evolving (Mejía-Salazar and Oliveira, 2018). Continued integration with certain technologies such as paper-based devices, microfluidics, smartphones and wearable technology can also be a key focus for these sensors to move forward as these fields advance and provide a clear path towards a simple, facile, portable and automated design (Guner et al., 2017; Liu et al., 2014a; Wei et al., 2017). Furthermore, substrates composed of new materials such as semiconductors, magnetic-materials and metamaterials are currently being investigated to manipulate optical properties involved with plasmonic materials (Mejía-Salazar and Oliveira, 2018). Research will also continue to be pursued for promising materials such as polymers and plastics that have the ability to create inexpensive devices (Brolo, 2012).

With future advancements in surface functionalization, miniaturization, lithography and nanofabrication, plasmonic-based field-friendly devices will be one of the most important players in the evolution of global healthcare. Their ability to provide rapid and personalized treatment regimens through screening of drug resistance can work to tip the scale further in our favour in the fight against infectious diseases. As such, with continued development of these technologies and integration with various microfluidics-based LOC platforms, they are one of the most important tools to positively affect the lives of the countless people living under the burden of infectious diseases worldwide.

Declaration of competing of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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