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A Review: Surface Plasmon Resonance-Based Biosensor for Early Screening of SARS-CoV2 Infection

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ABSTRACT Rapid viral diagnosis is essential to contain the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in the community and ensure effective patient management. However, the current gold standard for diagnosis of viral disease depends on the time-consuming molecular technique. Surface plasmon resonance (SPR) phenomenon has been widely applied in the analysis of biomolecular interactions and analytes detection, which is currently being investigated as a quick diagnostic method of numerous viral infections. In this regard, researchers have performed experimental studies dedicated to enhancing the sensitivity and specificity of the SPR sensor performance for utilization in the medical diagnostic field. In this review, we summarized various SPR application including the recent advancements and advantages of different types of SPR-based biosensor such prism-based, localized surface plasmon resonance (LSPR), fiber optic, optical grating, and optical waveguide for the detection of SARS-CoV2. We proposed various technical recommendations to improve the sensitivity, accuracy, time response, and cost-saving means of the SPR sensor. A special focus was set for sensitivity enhancement aspects in terms of the type of prism, nanomaterials, support layer with type and shape of optical fibers for early, swift, and ultra-sensitive detection of viral infection. With the highlighted impacts of SPR application, this review frames the current potential and challenges of SPR in comparison to the current gold standard of viral infection diagnostic strategy.

INDEX TERMS Fiber optic, LSPR, SARS-CoV2, SPR-biosensor, surface plasmon resonance, optical grating, optical waveguide, viral detection.

I. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) pandemic started in Wuhan, China before spreading globally through international travelers. The transmission of SARS-CoV2 between individuals occurs via hand shaking, direct contact with contaminated surfaces, fecal-oral transmission, or even through airborne contamination [1], [2].

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Conventional temperature screening at international borders has been unable to identify infected asymptomatic travelers who are carriers, thus failing to prevent the outbreak [3]. Furthermore, antigen-rapid test kit (Ag-RTK) screening at international borders is time-consuming [4]. It needs at least 15 min, which is counterproductive because it results in crowding [5]. Thus, minimally invasive devices with real-time responses, such as ''touch and go'' finger-print screening systems, have the potential to reduce the time required for identification, thereby enhancing the process of pre-isolation

and close-contact tracing [6]. It is assumed to have a higher accuracy compared to existing temperature scanning in addition to reducing airborne transmission [7]. However, the concentration of virus on the fingertips may be lower than in respiratory droplets [8]. The screening process might be limited by the current device. Hence, prompt viral screening in the lowest sample concentration such as in airborne respiratory droplets has become a priority to control the escalation of viral disease.

SARS-CoV2 present symptoms such as coughing, fever, body pain and severe acute respiratory failure [9]. Nearly all viruses take advantage of mucosal surfaces and use it as their initial entryway for infection. SARS-CoV2 exhibits massive gene expression infection levels to human lung epithelial cells compared to severe acute respiratory syndrome coronavirus (SARS-CoV), which may trigger an immune response [10]. Referring to the data from the World Health Organization (WHO), coronavirus disease 2019 (COVID-19) infection has exhibited an increasing trend, with more than 240 million cases reported and over 4 million deaths worldwide as of 19 October 2021.

Currently, the gold standard for detecting SARS-CoV2 is the Reverse Transcription – Polymerase Chain Reaction (RT-PCR) [11]. This strategy enables reliable diagnosis and provides adequate sensitivity for early detection, [12] but the results can only be obtained in 72 hours due to sophisticated laboratory procedures [13]. The identification and sequencing of the virus must be executed early during the start of the disease occurrence to be used as a template in the PCR analysis [14], [15]. Since the virus is able to mutate, the genetic variability in the viral genome between the primer and target sequences can yield false-negative results and disrupt the accurate diagnosis of SARS-CoV2 [16].

In comparison to RT-PCR, Ag-RTK can be used in point-of-care (POC) and deliver results within 30 min [17]. The cycle threshold (Ct) of RTK-Ag, also known as the detection limit, is valued at 30, which is equal to 300 viral copies of RNA. It could not detect a Ct value higher than 30. According to a study from the Korean Society for Laboratory Medicine, Ag-RTK exhibits 81% sensitivity and 11% sensitivity, with a Ct value of 23.37 for samples with a high and low viral load, respectively. However, Ag-RTK demonstrates 100% specificity, in which a positive result confirms that the patient is positively infected with the virus [18].

To create a high-performance virus identifying device that can operate in real-time, the device not only necessitates 100% selectivity, but also 100% sensitivity. This means the devices should be able to detect the virus at Ct of more than 30. To improve the sensitivity of the device, the sample collection timing, procedure, and transportation of samples should be improved [12]. Ag-RTK is useful for POC service but costly if used for mass screening at public places. Alternatively, optical biosensors offer an attractive replacement scheme for real-time viral detection since it can be integrated with artificial intelligence-based instruments, safe, user-friendly, and cost-effective without a nucleic acid amplification process [19], [20].

An emerging branch of optical biosensors called the surface plasmon resonance (SPR) has attracted the interest of investigators in evaluating interactions between biomolecules [21]; this is because of its label-free, real-time monitoring, and sensitive responses [22]. Prism-based SPR known as Kretschmann configuration is favored due to its simplicity, wherein SPR remains on a thin layer of metal film coated on top of a prism. Nonetheless, the conventional prism-based SPR sensor cannot be utilized for remote sensing applications due to the bulkiness of prisms. Localized surface plasmon resonance (LSPR) is a plasmon phenomenon generated without the presence of a prism by irradiating light on metal nanoparticles rather than a thin metal film in a prism-based setup [23]. It creates a strong electric field in the area of the nanoparticles. The characteristics of LSPR have facilitated the development of naked-eye detection through colorimetric detection [24]. Additionally, optical fibers have been employed by investigators as a more compact and affordable alternative for coupling excitation light to surface plasmons (SPs), since this offers more flexibility and lower costs [25]. As opposed to prism-based SPR biosensors, fiber optic SPR biosensors can be miniaturized, which is beneficial in the development of diagnostic POC devices [26].

Additionally, optical grating and optical waveguide can be used to materialize SPR [27]. Grating-based SPR sensor can be composed on single and multimode fibers using a phase mask and lasers [28]. In contrast, waveguide-based SPR sensor exploit the excitation of SPR in a slab waveguide at the surface of the sensing layer [29]. Without the bulkiness of a prism, both grating-coupler and waveguide coupler SPR sensor are feasible for miniaturization.

There are various reports on SPR-based biosensing for the recognition of viral infection due to its characteristics of rapid and label-free detection. In addition, it can be performed without specialized personnel. For instance, Sheh Omar *et al.* fashioned a prism-based biosensor for the recognition of E-protein dengue virus (DENV) with 39.96 $^{\circ}nM^{-1}$ sensitivity [30]. NS1-protein of DENV has successfully been detected in approximately 5 min without the use of specialized training in handling SPR instruments [31]. Moreover, Funari *et al.* designed a biosensor based on LSPR, incorporating gold nanospike (Au nanospike) in an opto-microfluidic chip as a sensing layer for the recognition of antibodies specific to SARS-CoV2 S-protein [32]. The limit of detection (LOD) of the detection platform is 0.5 pM. Meanwhile, Zhao *et al.* have proven that the recognition of influenza A (H6N1), a side-polished fiber optic SPR biosensor, was achieved in 10 min with a detection limit of 5.14×10^5 EID_{50}/0.1 mL [33].

A detailed study of recent advancements of plasmonic biosensors for recognition of virus has been comprehensively reported elsewhere [34]–[38]. There has been thorough research on biosensors for POC COVID-19 detection but not specifically on SPR-based biosensors [6], [39]–[43].

Nevertheless, the information yielded from previous studies is crucial. This review focuses on the recent advancements of different types of SPR sensors such as prism-based, LSPR, and fiber optic sensors, for the detection of SARS-CoV2. A particular focus on sensitivity enhancement in terms of the type of prism, nanomaterials, support layer, and type and shape of optical fibers of SPR sensors for early, swift, and ultra-sensitive detection of viral infection will be addressed. This review provides insights that can promote the future development of swift, point-of-care COVID-19 diagnosis based on SPR optical phenomena.

II. BIOSENSING PRINCIPLE

The SPR phenomenon entails the changes of refractive index on the metallic sensing layer such as gold (Au), silver (Ag), or copper (Cu) at the interfaces of two varied media such as glass and liquid. It depends on the measurement of refractive index changes, as the immobilized biological receptors on the sensing layer captured the target analyte. The detector measures the intensity shift and produces the SPR signal which is proportional to the mass of material bound to the surface. The charged density of plasmon oscillations occurs as the metal-dielectric interface is expressed as surface plasmon oscillations [44]. The oscillations or the electrons generate surface plasmon polaritons (SPPs). SPR occurs when plane-polarized (p-polarized) light illuminates the metallic sensing layer under total internal reflection. For the prism-based sensor, the wavelength is dependence to the metal dielectric function [45]. Hence, different metals demonstrate effective SPR excitation in different wavelength. By incorporating SPR in biosensors, the biomolecule interactions between the immobilized ligand and target analyte can be monitored in real-time [45]. In waveguide coupled SPR sensor, the light is driven over extensive distances by TIR from light excitation directed to the guiding layer of a planar optical waveguide [46].

In comparison, LSPR involves a simpler setup that does not require a prism to couple the light [47]. Rather than SPPs that propagates on metal-dielectric interface, the SPPs vigorously accumulate on the surface of the metallic nanoparticles, which is called LSPR [48]. The signal of the resonance wavelength from LSPR is dependent on the shape and size of the noble metal nanoparticles as well as the medium around it [47], [49]. Because there is no prism, and nanostructures are used as opposed to thin film plasmonic surfaces, LSPR have the advantage of producing a more compact and miniaturized design. Due to the use of nanostructures rather than semi-infinite plasmonic surfaces, LSPR possesses a high surface-to-volume ratio for sensing surface-analyte interactions, which can be integrated into more compact and miniaturized SPR sensors. SPR and LSPR both rely on the refractive index of the surrounding media to generate spectral shifts [35]. Still, the nanoparticles utilized in LSPR are below the wavelength of incident light. The spatial resolution of LSPR can be intensified by scheming the geometry and composition of metallic nanostructures that yield the basis for colorimetric plasmonic biosensing [24].

Alternatively, SPR can be applied using optical fibers for virus detection via miniaturized platforms. Plasmonic fiber optic biosensors are a new class of fiber optic sensors that arise from the intersection of plasmonic phenomenon and fiber optics [47]. These consist of a plasmonic metal film coating in the fiber's unclad core area. The core-cladding structure of the optical fiber enables the electromagnetic wave inside the fiber to undergo total internal reflection, identical the fundamental of operating principle of a prism-based SPR sensor. The result of the fiber optic sensors can be obtained by monitoring the shift of the resonance peak in absorbance spectra [50]. It can be fabricated into different geometries that include unclad fibers, side-polished (D-shaped) fibers, tapered, and U-shaped fibers [26], [50]. Diffraction grating can be applied to optical fiber to create a grating based SPR sensor. A diffraction grating functions alike prism, capable of slicing light into parts dependent on wavelength. For example, fiber Bragg rating (FBG) probe that exhibit excellent sensitivity, and unaffected to electromagnetic interferences, suitable for POC screening application [51]. Fiber optic SPR sensors can be miniaturized, which is useful to detect samples that are in minute quantity or are costly. Miniaturized sensors are highly desired by researchers because they can aid in realizing the potential of on-site detection. A more detailed explanation of their sensing principle was noted in other research, [26], [44], [48] which is beyond the scope of this review.

III. SPR APPLICATION

Numerous studies in the literature found the SPR-based biosensor to be an effective, and rapid detector for different application, including in the context of food quality control, chemical gas detection, and biomolecule or analyte detection. In a food quality control context, it was reported that an SPR-based biosensor was able to detect formalin in a liquid solution [52]. It delivers swift results with excellent sensitivity of 98°/RIU and quality factor of 88.89 RIU^{-1}. More recently, an SPR sensor for formalin detection that exhibit improved sensitivity of 155.33°/RIU and quality factor of 21.00 RIU^{-1} was reported [53].

In another study, an SPR for glucose detection was presented. The sensors were tested with glucose concentration that matched with a normal person and a hyperglycemia patient, which were 70mg/dl and 235mg/dl, respectively [54]. Technically, it exhibits high sensitivity and selectivity in detecting the presence of glucose with various concentrations and can sense an exceptionally small concentration of glucose. The Cu/Chitosan SPR sensor offers great potential for a low material cost, ease of handling, low cost, and miniaturized form.

The use of SPR-based fiber optic sensors for the detection of nitrogen dioxide (NO_2) gas was reported recently [55]. A high sensing response was reported for the zine oxide/gold (ZnO/Au) SPR sensors, with an increase in the concentration

range from 0.5 to 250 ppm of NO2 gas. Aside from these, a group of investigators developed an SPR sensor for the detection of glucose and various gases [56]. Recently, FBG SPR-based sensor were developed for real-time detection of E. coli bacteria, strain, pressure, humidity, and temperature [57].

Recent explorations have considered the SPR-based sensor for medical diagnostic applications. For example, Widoretno *et al.* developed an SPR biosensor for the detection of dengue NS1-protein for dengue virus [31]. This protein is vital for the RNA replication of this virus. Nilsson and colleagues utilized recombinant HA protein such as A/H1N1 immobilized on the Au surface of the SPR sensor for the quantification of hemagglutinin (HA) [58]. The proposed sensor demonstrated high precision and excellent sensitivity with less analysis time. Besides that, a waveguide coupler SPR sensor with a sensitivity of 2581 nm/RIU is fabricated [59]. The sensor proves its feasibility to operate in visible wavelength range. It is appropriate for sensing biological analytes in aqueous media such as hepatitis B virus (HBV), and glucose.

A group of researchers instantiated an SPR analytical system for the detection of SARS-CoV [60]. After sensitivity enhancement, the SPR sensor yield positive results for early screening of SARS-CoV. Another study as well demonstrated an SPR sensor that could detect anti-SARS-CoV2 antibodies in the nanomolar range within 15 min with high selectivity [61]. SPR sensors that are effective in the detection of SARS-CoV2 antigens have also been reported [62], [63]. The proposed design indicates high sensitivity and provides a relevant configuration for a label-free and real-time detection of SARS-CoV2.

Previous investigation has verified that SPR can be employed for a variety of applications. Furthermore, the described SPR has the potential to be a quick, sensitive, real-time, and label-free diagnostic tool.

IV. SPR BIOSENSOR FOR THE DETECTION OF SARS-COV2

A. PRISM-BASED BIOSENSOR

Being a highly effective optical practice, SPR can be applied in different fields, such as biochemistry, medical sciences, medical diagnostics, and biology [64]. Fig 1. illustrates the basic SPR sensor configurations based on the Kretschmann configuration, also known as a prism-based SPR sensor, which is preferred for its simplicity. Presently, there is minimal research on prism-based SPR biosensing for the recognition of COVID-19 infection [61], [65].

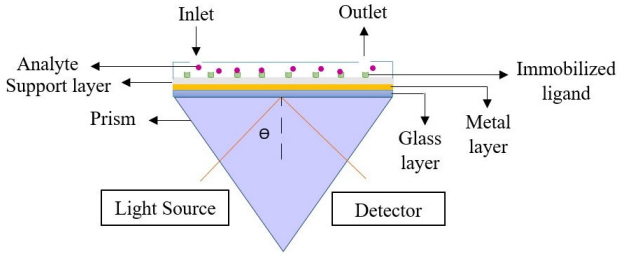


FIGURE 1. Conventional prism-based SPR biosensor setup.

A multilayer SPR biosensor consist of titanium dioxide (TiO_2), Ag, $MoSe_2$, graphene (C), and BK7 prism was constructed for the specific detection of SARS-CoV2 spike (S) protein [63]. Since the optical non-linearity enhanced at higher frequency but whole performance improved at lower frequency, the sensor operates at light wavelength of 633 nm. The authors reported that the highest sensitivity achieved was 194 °/RIU, with superior detection accuracy from the proposed configuration. A linear relationship between concentration and SPR angle shifts perceived for the concentration of S-protein ranged from 0.0001 to 10 nM. Previous investigations reported that the introduction of TiO_2 improved the sensitivity of the SPR sensor [66], [67].

Djaileb *et al.* reported on a prism-based SPR detection platform with peptide monolayer functionalized with SARS-CoV2 nucleocapsid (N) recombinant protein for the detection of N antibodies, specifically against SARS-CoV2 [61]. To ensure the feasibility of the sensor, undiluted human serum from the patient's oropharynx swab was tested. The developed device exhibited a high selectivity towards the N-protein, even when the SPR sensor was injected with different kinds of antigens, such as anti-prostate-specific antigens. The LOD of the sensor was roughly 1 μg/mL, with a response time of 15 min.

Peng *et al.* fabricated an SPR biosensor by integrating tellurene and carboxyl-functionalized molybdenum disulfide (MoS_2) layers with indium tin oxide (ITO) film [65]. Angiotensin-converting enzyme 2 (ACE2) receptors were immobilized on the MoS_2-COOH sensing layer, which is an ideal adsorption spot for the specific binding of S-protein. The specific binding interaction between S-protein and ACE2 receptor was described as an excellent linear response ensuring the feasibility of the sensor. This sensor exhibited an excellent linear detection range for S glycoprotein and SARS-CoV2 specimens that were ∼0–301.67 nM and ∼0–67.8762 nM, respectively. At incident wavelength of 1550 nm, the S protein were dissolved in running buffer with refractive index of 1.3345. After undergoing optimization, the highest detection sensitivity was discovered to be 8.4069×10^4 degrees.

An assembly of investigators created a multilayer SPR biosensor consisting of BK7 prism, Au, platinum diselenide ($PtSe_2$), and C for a highly sensitive detection of SARS-CoV2 S-protein [68]. The study reported a simulation comparison of a ligand-analyte setup involving monoclonal antibodies, S-protein, specific probes, IgG, IgM, and COVID-19 single-stranded ribonucleic acid (RNA) as analytes, respectively. Different setup was to determine the highest sensitivity arrangement. It was found that the detection of S-protein with monoclonal antibodies as immobilized ligand, exhibited the highest sensitivity, 183.33 °/RIU. The performance of the sensor was validated simultaneously using the transfer matrix method (TMM) algorithm and the

finite-difference time-domain (FDTD) method at plane wavelength of 633 nm, and the refractive index of 1.0. The simulation analysis proves that the proposed sensor could be a potential substitute for SARS-CoV2 S-protein detection.

Rather than merely for medical diagnosis, SPR can be used to evaluate the binding kinetic analysis of SARS-CoV2 with the ACE2 receptors to comprehend the virus-receptor recognition mechanism. For instance, an investigation focuses on the chimeric structure of SARS-CoV2 and SARS-CoV with its binding kinetics towards ACE2 receptors [69]. Based on the results from SPR analysis, SARS-CoV2 establishes a higher binding affinity to ACE2 receptors compared to SARS-CoV. These findings are significant as a guidance for researchers to develop intervention strategies that target receptor recognition by SARS-CoV2. Table 1 summarized prism-based biosensor for the detection of SARS-CoV2.

TABLE 1. Summary of prism-based biosensor for SARS-CoV2 detection in terms of their sensing layer, target analyte, sensitivity, LOD and time analysis.

Sensing materials	Target Analyte	Sensitivity	LOD	Time analysis	Ref.
Peptide monolayer and N-protein	Anti-N SARS-CoV2 antibodies	-	1 µg/mL	15 min	[61]
Tellurene, MoS2-COOH, ITO and ACE2 receptor	S-protein	8.4069 x 10^4 °/RIU	-	~10 min	[65]
TiO2, Ag, MoSe2 C, BK7 prism and CR3022 antibody	S-protein	194 °/RIU	-	-	[63]
BK7, Au, PtSe2, C and monoclonal antibodies	S-protein	183.33 °/RIU	-	-	[68]

B. LSPR BIOSENSOR

The difference between SPR and LSPR lies in the dimension of the plasmonic nanomaterials [22]. In LSPR, the light waves are imprisoned in nanoparticles which are smaller than the wavelength of light. The electromagnetic field remains localized in a nanoscale region around the nanoparticle-dielectric interface [70]. Fig. 2 displays the common LSPR setup without the use of a prism, as opposed to the conventional SPR setup. Generally, LSPR sensors are designed with metallic nanostructures, such as nanorods, nanoparticles, nanoislands, nanoshells, and others. Two classifications of LSPR-based biosensors were used. Firstly, were examined changes in refractive index when the LSPR peak wavelength shifts as the analyte binds to the ligand immobilized on the surface of nanoparticles. Variation in color were observed during LSPR shifting as the plasmonic fields of nanoparticles react with

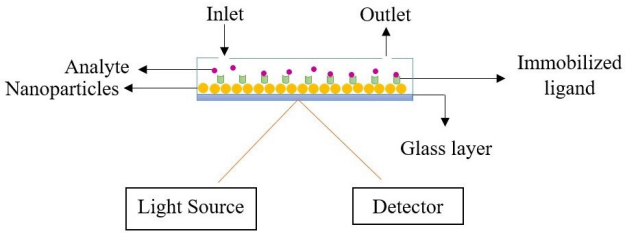


FIGURE 2. Typical LSPR biosensor setup.

the analyte [71]. In recent years, there have been various reports of LSPR biosensing for SARS-CoV2, which will be discussed in this section.

An opto-microfluidic sensing platform with Au nanospikes for the recognition of antibodies specific to SARS-CoV2 S-protein was developed by Funari *et al.* based on LSPR [32]. The feasibility of the sensor is evaluated using the diluted blood plasma of patients. The authors conducted a comparison study between the proposed sensor and existing conventional serological assays. The proposed sensor is capable of quantitatively detecting SARS-CoV2 antibodies in under 30 min which is faster than most conventional detection approaches using only 1 μL of plasma. The LOD is approximately 0.5 pM, comparable to other optical instruments for antibody detection [72].

A detection platform based on plasmonic photothermal effect (PPT) and LSPR phenomenon was fabricated for the recognition of the SARS-CoV2 viral sequences [73]. The gold nanoislands (AuNIs) sensing layer is functionalized with complementary DNA receptors, providing a sensitive detection by nucleic acid hybridization. The absence of the PPT unit from the sensor affects the LSPR sensing response; as a result, PPT enhances the hybridization kinetics of the viral DNA. The laser is set to 532 nm peak wavelength and 40 mW maximum optical power where the most steady and strong thermoplasmonic field were produced. The proposed sensor illustrates 0.22 pM LOD and specific detection for SARS-CoV2 compared to SARS-CoV.

A group of investigators designed a low-cost plasmon nanoarray SPR chip integrated in a generic microplate reader without the need for a prism or other optical coupling to excite the SPPs [74]. The functionalization of gold nanoparticles (AuNPs) was achieved with the immobilization of ACE2 receptors to specifically bind with SARS-CoV2 S-protein. The portable sensor can detect a quantity as low as 30 virus particles in under 15 min [74]. The authors noted that the characteristic spectral changes made it possible to detect the virus using SPR with high sensitivity.

To abolish the need for specialized personnel, nanoparticle-based colorimetric SPR sensor can be incorporated in a lateral-flow strip to design it as a POC device [22]. Moitra *et al.* created a naked-eye SARS-CoV2 recognition technique based on colorimetric SPR assay with the employment of AuNPs [75]. Colloidal AuNPs were capped with thiol-modified antisense oligonucleotides (ASOs) specific

for N-gene (nucleocapsid phosphoprotein) of SARS-CoV2 for the colorimetric detection of these RNA sequences. The sensor exhibits high selectivity when it enables the diagnosis of COVID-19 patients within 10 min using isolated RNA from oropharyngeal swabs at 0.18 ng/μL LOD.

In another comparable study, investigators established the effectiveness of a swift colorimetric assay for naked eye COVID-19 recognition [76]. The colorimetric RNA-based assay undergoes a validation test using clinical samples from COVID-19 patients that tested positive based on RT-PCR. It targets RdRp-specific genomic sequences of SARS-CoV2. The proposed assay displays cost-effective alternative and high sensitivity with LOD of 0.5 ng within a 30 min time frame. Specificity tests show high selective recognition of SARS-CoV2 against cervical DNA samples from infected patients. Table 2 summarized LSPR biosensor for the detection of SARS-CoV2.

TABLE 2. Summary of LSPR biosensor for SARS-CoV2 detection in terms of their sensing layer, target analyte, sensitivity, LOD and time analysis.

Sensing materials	Target analyte	Sensitivity	LOD	Time analysis	Ref.
Opto-microfluidic, Au nanospikes and S-protein	Anti-S-protein antibodies	-	0.5 pM	30 min	[32]
AuNIs and complementary DNA receptors	SARS-CoV2 genome sequences	-	0.22 pM	11. 67 min	[73]
Au, TiO_2, and SARS-CoV2 antibodies conjugated with AuNPs	SARS-CoV2	-	0.5 ng	30 min	[76]
AuNPs capped with thiol-modified ASOs	N-protein RNA sequence	-	0.18 ng/µL	10 min	[75]
AuNPs and RdRp oligo probe	SARS-CoV2 RNA sequence	-	30 virus particles	Under 15 min	[74]

C. FIBER OPTIC BIOSENSOR

Another example which highlights the potential of COVID-19 detection using SPR is fiber optics [35]. Fig. 3 depicts the typical fiber optic SPR-based biosensor configuration. Fiber optics could be a substitute for the bulky prism-coupling in the advancement of miniaturized instruments [77]. In the recent outbreak of COVID-19, researchers took advantage of its outstanding features to create POC instruments.

A novel technique for the detection of SARS-CoV2 N-protein was successfully employed using a plasmonic fiber optic absorbance biosensor (P-FAB) [78]. The proposed

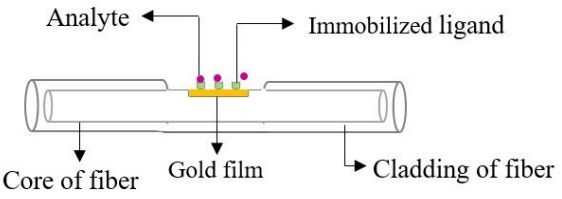


FIGURE 3. Typical fiber optic SPR biosensor setup.

sensor observes the optical power loss that propagated in a multimode U-bent fiber optic probe, wherein AuNPs with 20-60 nm thickness were immobilized followed by anti-N-protein monoclonal antibodies. The biofunctionalized probes were successfully utilized to detect the N-protein in the patient's saliva sample within 15 min.

Recently, a novel synthetic molecularly imprinted polymer (MIP) receptor was incorporated in an SPR D-shaped plastic optical fiber probe (SPR-POF) for the identification of SARS-CoV2 [79]. The authors executed preliminary studies by associating the results of nasopharyngeal (NP) swabs in universal transport media (UTM) and physiological solutions (0.9 % NaCl) with RT-PCR. The results display that the sensitivity of the fabricated sensor was higher than RT-PCR, with a response time within 10 min. In addition, the proposed sensor produces SPR shifts on positive samples diluted up to 500 times, proving that it can detect small viral concentrations.

Using the same SPR-POF probe from previous study, Cennamo *et al.* utilized polyethylene glycol (PEG) and gold nanorod (AuNR) interface deposited as a sensing layer [80]. Subsequently, a specific aptamer sequence was immobilized on the interface for the detection of SARS-CoV2 S-protein to create an aptamer-based platform. Based on the data from the supplementary file, the LOD is 37 nM, seven times better relative to LOD of previous research [79]. Preliminary tests were performed with diluted human serum, evidencing that the S-protein can be detected in 1:50 v/v diluted human serum with LOD of 75.26 nM.

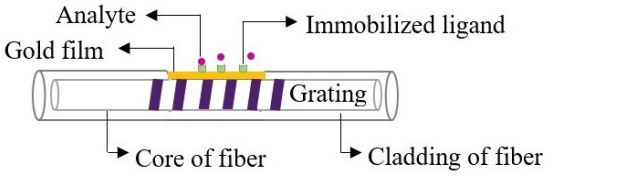
The ultimate advantage of fiber optics over conventional SPR biosensors is that the SPR probe can be miniaturized. Table 3 summarized fiber optic SPR biosensor for the detection of SARS-CoV2.

D. OTHERS

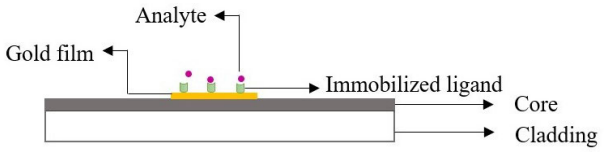
Several types of grating coupler investigated throughout the years are FBG, tilted FBG, and long period grating [28], [81]. This review will present examples on FBG SPR-based biosensor specific for SARS-CoV2 detection. The bare grating spot coated with metal ensuring SPs to occur which allows the sensor to execute label-free identification of viral infection [28]. On the other hand, optical waveguide can be fabricated for various functions, seemly the user's requirement. For virus detection SPR-based biosensor, optical waveguide can be utilized to splitting the lights into the desired working wavelengths [82], [83]. Fig 4. (a) exemplifies FBG SPR biosensor setup.

TABLE 3. Summary of fiber optic SPR biosensor for SARS-CoV2 detection in terms of their sensing layer, target analyte, sensitivity, LOD and time analysis.

Sensing materials	Target analyte	Sensitivity	LOD	Time analysis	Ref.
AuNP and anti-N-protein antibodies (U-bent fiber optic probe)	N-protein	-	0.5 ng	15 min	[78]
Au and MIP receptor (D-shaped)	S-protein	-	10^6 particles /mL	-	[80]
AuNR, PEG and aptamer, (D-shaped)	S1 subunit of S-protein	6.483 nm/μM	75.26 nM.	10 min	[79]



(a) FBG SPR-based biosensor setup



(b) Waveguide SPR-based biosensor setup

FIGURE 4. (a). FBG SPR-based biosensor setup. (b). Waveguide SPR-based biosensor setup.

Another means for non-invasive recognition of SARS-CoV2 was developed using Au/FBG probe [82]. The wavelength shifts and amplitude variance for patients with hyperinflammatory stage are 0.92 nm and 1.68 dB respectively. Whereas for patients at early stage of infection are 0.39 nm and 0.48 dB respectively. The results reveal wavelength and intensity of detected light changes even from samples of earliest infection. The simple biosensor displays swift recognition of SARS-CoV2 within 10 s in any stage of infection.

A multiplexed Au coated grating-coupled fluorescent plasmonic (GC-FP) biosensor was designed for identification of SARS-CoV2 infection in human blood serum and dried blood spot samples [83]. The fluorescence emission intensity was enhanced by the SPs created by the gold-coated chip which elevate the sensitivity of the biosensor. Test results were compared with ELISA and a Luminex-based microsphere immunoassay that proves excellent association. The constructed biosensor capable of detecting serum IgG levels against three different S-protein antigens (receptor binding domain, RBD; spike S1 fragment; spike S1S2 extracellular domain) and N-protein in under 30 min with 100 % selectivity.

Waveguide coupler is a different way to excite the SPs. Fig 4. (b) illustrates waveguide SPR-based biosensor setup. When light enters the waveguide region, the SP can be stimulated, and the coupling condition can be achieved when the propagation constants of the guided and SP modes are equivalent [84]. The wavelength peak shift will be measured with changes of refractive index. This approach of spectral interrogation differs from the angular interrogation approach used in prism-based or grating-based SPR sensors [85].

Recently, a planar-optical multi-mode polymer waveguide was fabricated to detect C-reactive protein (CRP) [86]. CRP is a high level of inflammatory biomarkers that can indicate the severity of the COVID-19 infection [87]. The sensor could detect biomarkers in the nM range after being optimized using gold nanoparticles (AuNPs). It resulted in a distinct shift in the SPR wavelength, with a sensitivity of 608.6 nm/RIU and resolution of 4.3×10^{-3} RIU. Aside from that, a white light LED was used for interrogation throughout the studies, demonstrating the sensor's potential to be employed as a POC device using a light source such as a smartphone.

FBG probe is robust and relentless against electromagnetic interference. Optical waveguide for SPR excitation offers miniaturization capabilities, high sensitivity, and vision of fabrication of multiple or multichannel sensors on a single chip [88]. The prospect of miniaturization for grating coupler and waveguide coupler SPR sensor are befitting POC viral screening process. Table 4 encapsulated other types of SPR biosensor for SARS-CoV2 detection.

V. ADVANTAGES AND LIMITATIONS OF CURRENT PLASMONIC BIOSENSOR

A. ANALYSIS ON PRISM-BASED SPR BIOSENSOR

Previous investigations have elucidated the fact that prism-based SPR biosensor allows for the label-free recognition for viruses [30], [61], [89]. It exhibits a simpler structure, ease of fabrication, biocompatibility, and high accuracy [63]. Additionally, SPR virus recognition based on antigen-antibody interaction is more sensitive compared to immunochromatographic, Ag-RTK, and ELISA techniques [90]. SPR elevates the surface sensitivity of the immobilized ligand to react with the target analyte.

One distinct weakness of prism-based SPR sensors is the need for external coupling to excite the SPPs. The light coupling tactic, where the prism is utilized as the light coupler can be used to generate enough energy [91]. The employment of prisms limits its capacity to be effective for miniaturization and remote sensing. Consequently, it leads to a greater power consumption. A conventional setup with Au and a prism is not sufficiently sensitive for certain application that require low sample concentrations [92], [93]. Au has become the ultimate choice as a metal layer in an SPR-based biosensor due to its

TABLE 4. Summary of others SPR biosensor for SARS-CoV2 detection in terms of their sensing layer, target analyte, sensitivity, LOD and time analysis.

Sensing materials	Target analyte	Sensitivity	LOD	Time analysis	Ref.
Au, C oxide, and anti-S-protein antibodies (FBG)	S-protein	-	-	26.67 min	[82]
Au, spike S1, spike S1S2, and N-protein (FBG)	Anti-S-protein and anti-N-protein antibodies respectively	-	1.6×10^3 copies /mL	30 min	[83]
Streptavidin-modified AuNP, aptamer and anti-CRP aptamer (Optical waveguide)	CRP	0.118 nm/nM	12.46 nM.	30 min	[86]

high stability in chemical medium and biocompatibility [94]. But Au is less sensitive compared to other types of metal such as Ag and Cu. However, Ag is unstable in a chemical medium, and Cu is prone to oxidation, which limits the functionality of the sensor [94]. In order to make prism-based SPR sensors more practical, aspects such as stability and higher sensitivity for low virus concentration identification are necessary. The addition of a support layer to the SPR setup can boost the sensitivity and stability of the sensor to be utilized at POC.

B. ANALYSIS ON LSPR BIOSENSOR

In LSPR structure, SPR can be achieved in the absence of a prism, unlike the predictable prism-based SPR sensor. It illustrates a high aspect ratio that permits a wider surface area interaction with immobilized ligands, promoting biomolecule sensitivity. LSPR utilized metallic nanostructures such as nanorods, nanoparticles, nanoislands, nanoshells, and others to produce SPPs [95]. Superior sensitivity evaluated by the refractive index changes and molecular binding were achieved due to widened plasmonic fields in the nanostructure. With LSPR, the geometric design and shape of the metallic nanostructures permit for an improvement of spatial resolution that allows for colorimetric biosensing [24]. Colorimetric assays have enabled advancements in the field of naked-eye detection [75], [76]. Since it only demands a light source and detection platform in the setup, it is advantageous for miniaturization.

Reports from previous studies have suggested that SPR-based sensors exhibit higher refractive index sensitivity than LSPR-based sensors, which can cause errors in experimental data [70]. The signal stability of LSPR sensors depends on the stability of the nanoparticle [96]. Since it uses metallic nanostructures in its configurations, it demands a thorough nanoparticle control technology. The application of nanoparticles in plasmonic biosensors results in size and shape dependent LSPR absorption with scattering bands. Hence, the size and shape of the nanoparticles must be meticulously formed to elicit the necessary optical response.

C. ANALYSIS ON FIBER OPTIC SPR BIOSENSOR

Fiber optic SPR sensors could magnify the wavelength modulation operation for optical excitation. It is suitable to be used for remote sensing, on-site monitoring, and in vivo measurements due to the smaller sample, low cost, miniaturization, and simpler structure [33], [97]. Fiber optics uses the core of the optical fiber to generate SPPs [26]. They are highly sensitive towards the small refractive index deviations presented by the biochemical reaction [98]. The integration of SPR in fiber optic sensors widen its application in the fields of biology, medicine, and diagnostics [50], [99]. It exhibits the capability to work in nanoscale and presents versatility in terms of design, power consumption, materials, and sensing performance.

There are two primary types of optical fibers, namely glass optical fibers (GOF) and plastic optical fibers (POF). GOF is lacking compared to POF in terms of availability, cost, robustness, flexibility, and ease of handling [100]. Hence, POF is favored for biosensor construction [78], [80]. Additionally, a conventionally shaped fiber optic SPR sensor, as illustrated in Fig. 3, is unsuitable for viral detection with low LOD [26]. POC devices demand a sensitive detection platform with a little analyte sample for fast screening. Thus, certain designs of fiber optic probes are unsuited. Specific shapes of the fiber optic probe are available to adapt to the user's needs, which will be discussed in the next section.

D. OTHERS

Exploitation of a single optical fiber to produce different resonant frequencies is feasible with different grating periods of FBG-based SPR biosensor [28]. From this, multichannel sensing is accomplished with the utilization of wavelength division multiplexing. Since SPR is generate without prism, FBG biosensor can be shrunken. These sensors are lightweight and mini-size convenient for POC antibody tests [101]. Miniaturized FBG probe are robust, invulnerable to electromagnetic intrusions, portable and sensitive fitting for biosensing applications [51]. Non-invasive FBG SPR-based biosensor offers plainer and ease of conducting process contrasted to performing swab test for RT-PCR. Subsequently, the threat to health care personnel is substantially diminished.

While there are certainly advantages grating-based SPR biosensor has to offer, the fabrication process of such sensors is complicated and expensive [102]. Based on previous report, human serum antibodies detection requires a temperature-controlling water bath to hasten the binding manner between antigen and analyte and stabilize the sensor's response time [82], [101].

Deploying an optical waveguide for SPR excitation opens the potential for miniaturize devices while maintaining excellent sensitivity. Besides, polymer materials are commonly employed in the manufacturing of optical waveguide devices. Hence, it offers more simplicity in manufacturing process and low production cost [88]. Recent studies had demonstrated that an optical waveguide-based biosensors have the potential to be used as a POC sensing system [86]. It exhibits promising result to be integrated with a low-cost light source, such as a flashlight from smartphone.

Yet, multi-mode waveguide structures have restriction in detecting refractive index changes of the surrounding media. This is because each mode of the waveguide structure coupled at a slightly different wavelength with the SPs, making the exact minimum point of the resonance grueling to perceive due to the very wide resonance [86]. This constraint was overcome in the same study by the binding of the AuNPs to the target molecule improving the sensitivity up to nm range [86].

VI. TECHNICAL RECOMMENDATIONS TO IMPROVE LIMITATIONS OF SPR BIOSENSORS FOR THE EARLY DETECTION OF VIRAL INFECTIONS

A. IMPROVEMENT OF SENSITIVITY AND ACCURACY

1) TYPE OF PRISM

The function of the prism in the conventional Kretschmann configuration is to couple a part of the power in the light source into the metal film [91]. Das *et al.* performed a simulation to compare which type of prism (BK7, SF10, and SF11) produces the most optimal detection platform for the detection of SARS-CoV2 S-protein. Based on the simulation studies, BK7 exhibits the ideal sensor resolution, with LOD of 7×10^{-5} RIU [103]. Nevertheless, SF10 prisms possess the lowest LOD at 4×10^{-5}. For incremental sensitivity, which is defined as a ratio of change in SPR angle to step-size change in refractive indices, BK7 yields the most excellent value, with 111.11 °/RIU. Hence, an SPR configuration with BK7 prism for the recognition of SARS-CoV2 S-protein is the optimal setup. The simulation investigation reveals that sensors with a BK7 prism can monitor the differences in refractive index effortlessly. This finding is supported by an investigation performed by Widayanti and Utomo [104]. They compared the performance of different types of prisms namely BK7, SF11, and 2S2G, in which it displays reduced sensitivity with an increasing refractive index. Hence, BK7 is selected as the optimum configuration since it possesses the lowest refractive index.

A multilayered SPR sensor consisting of Ag, BK7 prism, $MoSe_2$, C, and TiO2 were designed for the explicit detection of SARS-CoV2 S-protein [63]. A BK7 prism with a low refractive index value of 1.5151 is a crucial part of the configuration, acting as a light coupler to excite the SPPs [105]. Results from the comparison indicate that BK7 shows superior characteristics in terms of all aspects mentioned; sensitivity of 194°/RIU, quality factor of 54.0390 RIU^{-1}, and detection accuracy of 0.2702, surpassing other single- and multi-layered SPR setups. BK7 prism was mainly used as a light coupler compared to others, as shown in previous studies [106], [107]. In another similar study, a group of investigators utilized a BK7 prism with Au, PtSe2, and C for SARS-CoV2 S-protein recognition [68]. BK7 prism permits the highest accumulation of incident light at the Au surface to create optimal surface plasmon waves (SPW) at the interface. The highest sensitivity of 183.33°/RIU was achieved using BK7 prism.

Although prisms-based SPR sensors are large in size, high sensitivity can be achieved by selecting the prism with a suitable value of refractive index to acquire optimum SPR signals for protein biosensing [108]. Nevertheless, the employment of prisms in an SPR sensor eliminates the possibility of miniaturization. Another possible approach to scale down an SPR sensor involves the application of nanomaterials in LSPR configuration, fiber optics, optical fiber grating and optical waveguide. Table 5 summarize the performance parameters of BK7, SF10, SF11 and 2S2G prisms from reported studies. We can see that BK7 displays excellent sensitivity but poor resolution. However, its low refractive index is valuable to be employed in SPR setup for protein detection [68], [105].

TABLE 5. Types of prism with their performance parameters with Au metal film from previous reported studies.

Type of prism	BK7	SF10	SF11	2S2G
Refractive index	Low, n=1.51	Moderate, n=1.72	Moderate, = 1.76	High, n=2.29
Sensitivity	Excellent	Moderate	Moderate	Poor
Resolution	Poor	Poor	Poor	High

2) NANOMATERIALS

For the past few years, the advancements in nanomaterial-based biosensors for virus detection have been reported due to increases in detection accuracy and fast response. This section elaborates on the exploitation of nanomaterial for sensitivity enhancement in LSPR-based biosensors.

As part of a simulation study to create an SPR sensor with ideal configurations for specific S-protein detection, Das *et al.* model a sandwich plasmonic biosensor with AuNR conjugated to S-protein antibodies, which are immobilized on the Au nanosheet sensing layer [103]. AuNRs are elongated colloidal plasmonic metal nanocrystals [109]. It can refine the output signal via signal amplification, which in turn enhances the sensitivity of the prism-based SPR sensor. AuNR that exhibit peak absorbance near the working wavelength could maximize the coupling of local electric fields and the evanescent field at the sensing layer. Based on simulation results, the distance between the nanosheet and AuNR affects the evanescent field. Hence, it should be minimal to ensure that finest evanescent fields are produced. Based on a review

study, nanorods has the highest refractive index sensitivity, followed by triangles and spheres [110].

A dual plasmonic biosensor with the incorporation of PPT effects and the LSPR phenomenon on a AuNI chip enables encouraging advancements for POC SARS-CoV2 diagnostic platforms [73]. A thermally de-wetted Au was assembled on the BK7 glass substrate and then onto the two-dimensional (2D) AuNI. The exploitation of AuNI aids in designing a highly specific detection platform, which is crucial in infectious disease management. The LOD of 0.22 pM was achieved, creating a highly sensitive, real-time response and label-free detection platform. The excellent sensitivity is because of the escalating plasmonic fields in the AuNI nanostructure [17]. Subsequently, it produced accurate discrimination between the variation of gene sequences.

A group of researchers designed an opto-microfluidic biosensor consisting of Au nanospikes on glass substrate with a thin layer of chromium (Cr) [32]. The sensor is integrated with the microfluidic chip coupled with a reflection probe [32]. The Au-coated glass substrate was cut, cleaned, and dried prior to the electrodeposition (ED) process. The ED process could influence several of the nanostructure's characteristics, such as the shape and size to produce uniform Au nanospikes that have the most optimal optical properties [111]. Based on the scanning electron microscopy (SEM) results, ED conditions at 480 s produced the most regular and uniform Au nanospikes and became the protocol. The Au nanospikes with self-assembled (SAM) alkyl-thiols were functionalized with S-proteins of SARS-CoV2 to allow the specific detection of antibodies against it. With an LOD of 0.5 pM, the proposed sensor is a compact device, easy to maneuver, and suitable for POC tests.

In terms of naked-eye detection, colorimetric assay based on nanoplasmonic biosensor is a simple, and reliable biosensing technique. Moitra *et al.* designed a colorimetric biosensor using AuNP with thiol-modified ASOs [75]. The feasibility of the proposed sensor was tested from an RNA sample of COVID-19 patients taken from oropharyngeal swabs. Due to the presence of targeted RNA sequences in the sample, the AuNP-ASOs nanostructures selectively attached themselves, causing a red shift by the SPR phenomenon.

Alike to Moitra's research, Kumar *et al.* exploited the SPR effect of AuNPs by fabricating colorimetric assay for the quick detection of unamplified COVID-19 RNA in human samples [76]. They successfully evidenced highly sensitive detection assay for RdRp genes of SARS-CoV2 in under 30 min with LOD of 0.5 ng. Naked-eye detection is made possible with nanostructures that enhance the sensitivity and selectivity of the sensor.

Because of the SARS-CoV2 outbreak, POC diagnostic methods have become more essential to manage the disease before it progresses further. Au-based nanostructures have the potential to become a low-cost stand-in that offers the same (or a superior) level of sensitivity. Huang *et al.* constructed a POC nano-plasmonic sensor for the rapid detection of SARS-CoV2 S-protein with AuNPs-labeled ACE2-protein [74]. The implementation of AuNPs revamps the sensitivity of the sensor and allows for convenience detection in single-step sandwich immunoassay as opposed to a bimetallic sensing layer. The significance of thin film AuNPs is the ability to preserve uniform surface composition. The results of SEM validate the uniformity of the AuNPs on the substrate where contrasting colors of the water drops on the substrate compared to those in air were witnessed. The high sensitivity of SARS-CoV2 recognition was accomplished due to the characteristic's spectral changes.

In another study that utilized AuNP conjugated with specific antibodies to S-protein of SARS-CoV2, the authors highlighted the invention of a miniaturized plasmonic biosensor for the detection of S-protein, using toroidal electrodynamics concepts [112]. The proposed sensor exhibits the ability to tolerate robustly confined plasmonic modes with ultranarrow line shapes in the terahertz (THz) frequencies, thereby lowering the LOD. From the transmission profile to evaluate the sensor performance with functionalized AuNPs, the sensor indicated enhanced sensitivity as the binding strength of biomolecules was upgraded. The presence of AuNPs climaxes a crucial element of conjugation with the antibody to capture the target analyte.

Due to exceptional physicochemical properties, Au-based nanostructures have been widely employed for biomedical applications [113]. They have been exploited as the signal transducers in terms of optical signal amplifiers, current amplifiers, and resonance light scattering to fabricate biosensors for virus detection [95]. The benefits of the nano-plasmonic biosensor over the conventional diagnostic device include miniaturization, low cost, fast diagnosis, low amount of analyte for analysis and lower power depletion [114], [115]. LSPR integrated with the PPT effect boosts the hybridization kinetics, enabling accurate discrimination between the variation of gene sequences and increasing detection accuracy [73]. Additionally, incorporating LSPR with opto-microfluidic sensing platform aids in attaining an SPR sensor with low LOD [32].

3) ADDITIONAL SUPPORT LAYER

Support layers have been introduced into the SPR setup for sensitivity reinforcement. A group of analysts fabricated an SPR biosensor with tellurene, MoS_2, and ITO film for the highly selective detection of SARS-CoV2 S-protein [65]. ITO film is reported to have a great ability to excite the electron in the metal film, even in the absence of a prism coupler, allowing ideal photon adsorption and wide-field improvement [116]. The authors exemplify the utilization of BK7 glass interlayers to boost the detection sensitivity, since ITO film is typically deposited on BK7 glass substrate.

Platinum diselenide ($PtSe_2$) and C were used in a reported investigation for the specific detection of S-protein [68]. $PtSe_2$ is a 2D material made from transition metal dichalcogenides (TMDC) that exhibits superior optical properties, such as excellent carrier mobility and a tunable band gap due to strong interlayer activity [117]. The PtSe2 layer is an

emerging 2D group of 10 TMDC that has intriguing optical attributes, tunable bandgap, phase transition, and superior electron mobility [118]. SPR sensors with Au/PtSe2 arrangement demonstrate excellent performance [117]. Conversely, C helps to boost interactions between S-protein and immobilized mAbs. In the proposed sensor, five layers of C added yield the maximum efficiency [119]. As a result, the combination of $PtSe_2$ and C is capable of engineering a highly sensitive conventional prism-based biosensor [120].

In an investigation, the authors explored the use of oxide layers in the SPR setup for SARS-CoV2 S-protein biosensing to elevate the sensitivity [63]. Specifically, TiO_2 was found to be the most capable of maximizing the sensor's sensitivity among silicon dioxide (SiO_2) and tin oxide (SnO_2) [66]. The greatest shift of the dip in reflectance curves was reported with TiO_2. It can be incorporated as an adhesion layer for the nanostructures utilized in the SPR sensor, which makes them mechanically stable. TiO_2 illustrates an exceptional light-trapping ability that in turn conjures more SPs and increases the resonance angle with its sensing capability [67]. Oxide layers on metal surfaces provide protection against corrosion.

The authors also verified the usage of C as a support layer to boost the sensitivity of the SPR sensor [63]. The large surface area of C helps in the binding process between immobilized CR3022 antibodies with the S-protein. In addition, C is a preferred material among researchers due to its magnificent properties, such as its wide surface area, vigorous molecule adsorption, excellent carrier mobility, ease of fabrication, and superior optical properties [121], [122].

The support layer is not responsible for producing resonance electrons of the SPs, unlike the metal layer. Instead, the function of the support layer is to enhance the sensitivity of the sensor by providing a larger surface area to improve molecular adsorption, stability from corrosion, and detection accuracy.

4) TYPE AND SHAPE OF OPTICAL FIBERS

By altering the shapes of the fiber optic SPR probes (e.g., D-shaped [79], [80] and U-shaped) [78], the performance of the sensor could be improved to achieve an ultra-sensitive biosensor by enabling the interaction of propagating light in the optical fiber with the medium. The U-shaped probe could bring the incidence angle with the normal to the core-cladding interface closer to the critical angle. Greater evanescent wave interactions with the environment medium were produced from the U-shaped fiber optic sensor compared to straight fiber optic sensor with 10-fold enhancement of sensitivity. It permits a simplified setup, ease of creation, and improved sensitivity.

A study performed by Gupta and Verma exemplified that the sensitivity increases as the bending radius decreases, up to a definite value before it decreases. It is crucial to select an optimal value of bending radius where the sensitivity is the highest. Up to a certain level, as the sensitivity increases, the detection accuracy decreases from the broadening of SPR dip. However, since the maximum sensitivity acquired was a few magnitudes higher than the fiber optic SPR sensor with the tapered probe, the loss is negligible. Additionally, using a support layer such as MoS_2 or C can improve the detection accuracy [123], [124]. A group of investigators utilized a multimode U-shaped fiber optic SPR probe with AuNP for the specific detection of SARS-CoV2 N-protein. For the validation of the investigation, the probes are used to detect N-protein in human saliva samples; this was successfully performed in 15 min, thereby proving its effectiveness.

Conversely, D-shaped fiber optic SPR probes entail a small amount of analyte for measurements suitable for application with low LOD [50]. D-shaped fiber optic SPR probes exhibit a wide sensing area. It provides a better performance for biosensing applications (562). Presently, investigators have taken advantage of its benefits for the detection of SARS-CoV2. For instance, Cennamo *et al.* fabricates a D-shaped POF integrated with a novel MIP receptor for SARS-CoV2 S-protein recognition. Comparison exploration illustrates that the sensitivity of the fabricated sensor was higher than RT-PCR, with a response time within 10 min. The shifting SPR curves were still visible for positive samples diluted up to 500 times, proving their capabilities to detect low viral concentrations. Follow-up studies were executed with PEG and AuNR as sensing layers functionalized with specific aptamers to increase the sensitivity of the sensor. Validation studies were conducted with diluted human serum in which the S-protein can be detected in 1:50 v/v diluted human serum with LOD of 75.26 nM.

B. IMPROVEMENT OF TIME RESPONSE FOR REAL-TIME ANALYSIS AND APPLICATION

A minimally intrusive device with an instantaneous reaction, such as a ''touch and go'' fingerprint-type screening system is preferred to identify viruses such as SARS-CoV2. According to former studies, the existing SPR biosensor's time response is still lengthy. The shortest available time analysis is around 10 min [125]. Although it is quick compared to the available detection means, an instant diagnostics system is still vital to accelerate the diagnostic results. Among SPR schemes, array SPR imaging (SPRi) is one of the primary practices for analyzing affinity interactions in real time. The SPRi system is constructed by combining the configuration of an interrogation technique with a charge-coupled device (CCD) [126]. The CCD camera will record images of the chip and gather signals from sensorgrams [125].

The real-time monitoring of bovine serum albumin (BSA)/anti-BSA binding interactions at varied concentration levels has been studied by Wong et al [127]. A 2D array of antigen dots with varying immobilization concentrations are constructed on the Au sensor surface. As an analyte containing the target antibody was introduced into the flow cell, the SPRi system monitored the antigen–antibody binding interactions at each antigen dot in real-time. The signal was then transferred to a computer that uses graphical software to evaluate the SPRi pictures in 2D format.

Bak *et al.* used the same SPRi setup [126]. However, instead of using the conventional wavelength-scanning white light source, the team had employed a wavelength-swept laser. The high sweeping rate of the wavelength-swept laser enabled a high scan rate in their SPRi system, with a real-time scan rate faster than 12Hz. With a higher frame-rate camera, it was believed that a quicker scan rate would be achievable. The SPRi setup, however, is limited to the intensity interrogation method [126], [127]. Instantaneous measurement of the SPR dip in the angle and wavelength interrogation SPRi must be explored.

C. REDUCTION OF MANUFACTURING AND APPLICATION COSTS

Commercial SPR sensors on the market still involves a high-cost investment, components, and operations, rendering them unaffordable for implementation for POC or laboratory settings [128]. To realize a desirable low-cost sensing system, several configurations or modifications have been suggested in several papers. Rather than Au or Ag metal, Cu is another cheaper alternative metal. Cu can produce a finer resonance and a narrower plasmonic signal, resulting in increased sensitivity. However, it is susceptible to oxidation, similar to Ag; therefore, a protective layer of indium tin oxide ITO has been placed over the Cu layer to address this issue. This proposed configuration outperforms Au and Ag with the similar protective layer. Furthermore, the preparation of metal layers must be considered, as certain metals, such as 2D nanomaterial layers, are highly complex and costly to prepare [129].

Most of the strategy used for depositing metal film onto a substrate are time-consuming and expensive, complicating the overall metal film fabrication process. Xia *et al.* proposed a means to effectively prevent these issues [130]. A scheme known as the one-step sputtering method was adopted where the Au-Ag alloy target was utilized with the same mass composition to sputter Au-Ag alloy film directly onto a glass substrate as a sensitive layer to construct an SPR sensor chip. This is a simple approach to prepare sensing chips in bulk.

The absence of a prism in LSPR and plasmonic fiber optics could result in a cheaper alternative compared to the conventional prism-based SPR. For fiber optic SPR, Cennamo *et al.* suggested using POF rather than the conventional silica optical fiber for low-cost sensing system [131]. The POF have the advantages of simpler to fabricated due to their high flexibility and ease of manipulation [50], [131]. A D-shaped POF configuration was proposed by Arcadio *et al.* [132]. The fibers are used merely to connect the simple sensor chip with a light source and a detector. A similar design was employed recently by Cennamo *et al.* for the detection of SARS-CoV2 [70]. This low-cost and easy-to-implement fabrication procedure for the POF-SPR device has the potential to be industrialized in the future.

A polarized helium-neon laser (He-Ne laser) is the conventional light source for the SPR setup. This gas laser has a bulky size and high-power operation laser [128]. Another option that we can opt for is the polychromatic solid-state lighting technology, such as a laser diode, LED, and OLED. Because of its tiny size, this technology is not only a less expensive option, but it may be used to achieve smaller designs [128].

D. POSSIBILITIES OF INTEGRATING WITH AI-BASED DEVICE

For the past two years, AI technologies have been a significant tool to enable a COVID-19 response that assists in clarifying the virus's evolution, accelerating drug treatments, and preventing the virus's spread through contact tracing. Many countries such as Malaysia, Singapore, Austria, and China execute contact tracing by identifying close contacts and sending out warning messages for isolation automatically. The integration of SPR sensors with AI will contribute to the advancements in healthcare systems, including remote sensing to places that are difficult to reach.

AI technology is extremely effective for diagnostic improvement and the prediction of data from the SPR sensor. It can assist in data filtering and analysis, thereby reducing the number of decisions made by humans. Data from sensorgrams, for example, was used as a data set for a machine learning approach [133]. The sensorgram depicts real-time changes as well as refractive index changes and resonance position shifts after specific ligand–analyte or antibody–antigen interactions occur in the SPR sensing layer. The algorithm proposed uses TSD and k-NN to characterize, categorize, and recognize the sensorgram and hypothesis testing to identify the substances present.

Although there remains a scarcity of resources and research on this AI-based technology, we believe it can be combined with SPR to yield a real-time result. Additionally, these intelligence features can help with automated testing, which can aid in quicker virus diagnosis. As a result, healthcare practitioners will have a greater chance of containing the epidemic.

VII. CONCLUSION AND FUTURE PERSPECTIVE

It has been found that airborne viral transmission through respiration droplets and aerosol can cause infection. Respiratory size droplets from breathing or speaking, which are 0.8 to 1.8μm, showed the highest concentration in the air compared to the larger droplets [8]. Since the Ag-RTK can detect approximately 300 viral copies, it might be unable to recognize the virus present in the small respiratory droplets circulating in the air. Hence, if the optimal SPR biosensor can detect the viral RNA from the skin surface, assuming that the amount of viral RNA on the skin surface is less than 300 copies, it can be used as a non-invasive screening device in high-risk public spaces such as airports, supermarkets, or schools. Lately, SPR sensors that can be used for detection of SARS-CoV2 associated antibodies have been developed [61]–[63]. The portability of the SPR instrument will allow the deployment of this practice in the field for on-site measurement.

Prism-based SPR biosensor without additional support layers yields poor adsorption of biomolecules, which diminishes the sensitivity of the sensor. The sensitivity level of the sensor can be upgraded with the installation of a correct prism and support layer such as an oxide layer, ITO film, and C. Among various prisms reported, BK7 exhibits superior performance with excellent sensor resolution [103], low refractive index [104], and high detection accuracy [105]. Oxide layers such as TiO_2 can help to generate more SPs, which elevate the resonance angle and its sensing capability [67]. ITO film provides a protective layer that prevents corrosion and is an ideal photon adsorption with wide-field enhancement. Conversely, C has a wide surface area that assists in molecular adsorption by providing a wide refractive index change at the C-metal layer interface. These support layers can boost the sensitivity of the prism-based sensor to achieve the lowest LOD.

Though a predictable prism-based SPR configuration can achieve excellent sensitivity with an optimal setup, it operated in micro-scale and could not be minimized to nanoscale. Otherwise, LSPR and fiber optic SPR biosensors can be shrank. LSPR can perform real-time virus infection monitoring in nanoscale since it only obligatory a light source and a light detector. The SPPs induced on the nanoparticle surface create a strong electric field localized within the nanoparticles, which improves the sensitivity of the sensor [134]. Nanomaterial-based LSPR sensors that are small, brilliant sensitivity, label-free detection, less energy consumed, and low-cost setup, which is desirable for on-site prompt viral detection. Besides, they deliver the basis for colorimetric plasmonic biosensing when naked-eyed viral recognition is possible.

Moreover, fiber optic SPR sensors can enlarge the wavelength modulation operation for optical excitation. Since there are no electrical connectors, there are no electrical interferences, making them a robust and safer option than electrochemical biosensors. Fiber optic SPR biosensors can replace the prism-coupling in the advancement of miniaturized viral detection instruments [77]. For smaller sample concentration, they impart a low cost, miniaturization, and simpler structure for ultra-sensitive viral detection [33], [97], with immunity to electrostatic and electromagnetic interferences [135]. Additionally, implementing AI aids in the detection, diagnosis, and prevention of the spread of the virus.

Grating coupler and waveguide coupler expands the field of small-scale SPR biosensing. Fiber grating couplers offers high resistance to electromagnetic interference and admirable sensitivity. On the other hand, the integration of waveguide coupler permits high-density and compact optical sensor [29]. Both sensors are portable, which is promising for on-site biosensing practices.

Based on this research, we can conclude that SPR-based biosensors exhibit exceptional characteristics, for quick and specific analytical method of SARS-CoV2 early detection. This comprehensive review discusses the current SPR application. Furthermore, it underscores recent advancements of prism-based SPR, LSPR, fiber optic, optical grating, and optical waveguide SPR biosensors for the early detection of SARS-CoV2. A special focus was placed on the sensitivity enhancement of SPR biosensor towards a swift and ultra-sensitive virus infection diagnosis, despite its small size. This review will aid in the future development of a rapid and ultra-sensitive SPR detection platform for the specific detection of viral infections.

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