Portable Sensing Devices for Detection of COVID-19: A Review

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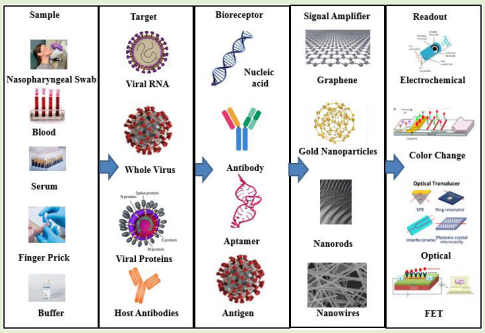
***Abstract*—The coronavirus pandemic is the most challenging incident that people have faced in recent years. Despite the time-consuming and expensive conventional methods, point-of-care diagnostics have a crucial role in deterrence, timely detection, and intensive care of the disease's progress. Hence, this detrimental health emergency persuaded researchers to accelerate the development of highly-scalable diagnostic devices to control the propagation of the virus even in the least developed countries. The strategies exploited for detecting COVID-19 stem from the already designed systems for studying other maladies, particularly viral infections. The present report reviews not only the novel advances in portable diagnostic devices for recognizing COVID-19, but also the previously existing biosensors for detecting other viruses. It discusses their adaptability for identifying surface proteins, whole viruses, viral genomes, host antibodies, and other biomarkers in biological samples. The prominence of different types of biosensors such as electrochemical, optical, and electrical for detecting low viral loads have been underlined. Thus, it is anticipated that this review will assist scientists who have embarked on a competition to come up with more efficient and marketable in-situ test kits for identifying the infection even in its incubation time without sample pretreatment. Finally, a conclusion is provided to highlight the importance of such an approach for monitoring people to combat the spread of such contagious diseases.**



***Index Terms*—COVID-19, SARS-CoV-2, point-of-care diagnostics, portable biosensors.**

I. Introduction

ACCORDING to the latest data, more than 55.6 million people have been infected by coronavirus disease 2019 (COVID-19) all around the globe since its first emergence in December 2019 [1]. This hazardous pandemic impacted all aspects of peoples' everyday lives and hindered the most routine activities to a level that was not even foreseeable before [2]. Besides the considerable limitations of international transportation, quarantine and social distancing policies have been applied in most of the nations [3]. However, these strategies cannot be a long-lasting solution. They will have detrimental impacts on the economy, education, food system, and even mental health [4]. It has devastated jobs and positioned millions out of employment. It is noteworthy that, even the strictest rules are not controllable and governments are not able to prevent the violations in the long-term [5]. It has become a challenge to control its ever-increasing transmission speed and make long-term plans to manage the problems it causes [6]. This problem becomes even more vital when talking about health care professionals [7]. Without accessible rapid diagnostic technologies, it is not easy to govern this lethal outbreak [8]. The currently used methodology for detecting COVID-19 is Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) which targets the viral genome in the nasal and nasopharyngeal samples. Although, it is considered the key standard in sensing the virus, a rapid, cheap, and easily available system is needed to determine the presence of the infection during the incubation period to provide enough time for adapting the desirable treatment process and curb its high spread rate [9], [10]. The other diagnostic methods such as CT imaging, nucleic acid tests, gene sequencing, and serological assays also lack the required promptness, cost-effectiveness, and ease of use in a point-of-care (POC) condition [11]. More importantly, their false-negative results necessitate the use of a combinatory detection techniquewhich itself increases the complexity and cost [12]. Given the mentioned constraints of the conventional approaches and the demand for a real-time, portable, and ultra-sensitive alternative for early detecting and monitoring the progression of the infection, it will worth introducing the biosensor technology which is one

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of the evolving studies throughout the recent years [13], [14]. Knowing that this epidemic can be intelligently regulated by the advantages offered by the novel tailor-made biosensors, researchers can think of innovative ways for designing a highly specific system for detecting SARS-CoV-2-related biomarkers [15]–[17]. This crown-shaped particle is an enveloped, single-stranded RNA virus that encodes spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins [18]. The surface S protein is considered one of the main biomarkers of the virus since it facilitates the virus's entry to the host cells [19]. Whereas the integral E protein which is responsible for the viral life cycles seems to be the most antigenic target for biosensing [20]. Also, the produced antibodies in the patients' biological fluids against the virus can be one other alternative target [21]. Similarly, the viral genome is another potential indicator of the virus's presence [22]. By employing specific biorecognition elements (BREs) like antibodies, antigens, proteins, whole viruses, nucleic acids, and aptamers, precise biosensing systems can be designed for spotting the SARS-CoV-2 [23], [24]. There are several classifications of biosensors that are capable of detecting tiny amounts of the target using low volumes of the sample [25]. Here we reviewed different categories of portable biosensing platforms which are developed recently for detecting the novel coronavirus 2019 and also the previously proposed systems for identifying other types of viruses. Their general aspects and core strategies were discussed comprehensively based on the most recent research outcomes. These portable devices have the required adaptability for being redesigned to recognize not only COVID-19 but also other disease-specific biomarkers and even future pandemic-causing pathogens. Furthermore, their portability, scalability, and simple fabrication process pave the way for their facile mass production. They can be easily available even for people from developing countries. It facilitates home diagnostics and allows remote detection without the need for skilled laboratory personnel and expensive equipment. Different techniques such as electrochemical, optical, surface plasmon resonance (SPR-based), and field-effect transistor (FET-based) biosensors were addressed. Lastly, a conclusion was provided summarizing the remaining challenges and prospects.

II. Different Types of Biosensors

A. Electrochemical

One of the most commonly used biosensors for detecting viral particles is electrochemical sensors [26]. Owing to their strong correlation with advancements in cost-effective microelectronic circuit designs and interrelatedness with standard readout systems, they can be fabricated through a simple and low-cost process [27]. Besides, these reliable and compact tools enable the detection of an analyte in a small volume of complex samples in a highly accurate, POC, and real-time manner which is desirable for medical diagnosis applications [28]. In order to boost the efficiency of the biosensor, it is vital to increase the signal-to-noise ratio which is possible by shrinking the size of the system by using nanostructures in their design [29]. The cooperation of nanotechnology and bioelectronics paved the way for the emergence of nanoscale

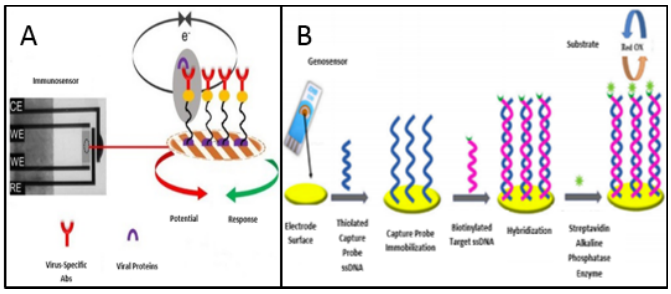

Fig. 1. Configuration of A. an electrochemical immunosensor for detecting viral particles, B. a genosensor for identifying viral genome [41], [42].

devices with higher accuracy in comparison to conventional systems [30]. By reducing the size of substances toward the atomic levels, their electrical characteristics become more responsive to external variables [31]. Their miniaturized sizes which are proportionate to the dimensions of the target, enable the identification of single molecules. Generally, this electrochemical reaction would result in a change in current, potential, impedance, or conductive properties of the medium which is categorized in *amperometric, potentiometric, impedimetric*, and *conductometric* types of sensors, respectively. There is also one other category called, *field-effect*, in which the current is measured at the gate electrode of a transistor. One of the most effective factors in the enactment of the electrochemical biosensor is the electrodes. Since the investigated reaction is occurring in their immediate vicinity [32]. That is why it is essential to choose the appropriate size, material, and surface functionalization in order to optimize the recognition capability of the electrode [33]. Typically an electrochemical measurement is conducted by three electrodes namely, reference (sustains a constant potential), auxiliary (facilitates the appliance of a current to the working electrode by connecting it to the electrolyte), and working (serves as the transducer) electrodes. Gold, carbon, platinum, fluorine-doped tin oxide, and silicon compounds are among the most favored materials for fabricating electrodes [34]. The importance of choosing the best material for the electrode is revealed when it comes to optimizing the double layer capacitance, the speed of the electron shuttle, and the surface modification [35].

Having said the general aspects of electrochemical biosensors, they are frequently utilized for the identification of viral particles [36]. Due to their portability, short response time, ultra-sensitivity, ease of use, cheapness, compact size, and low limits of detection (LOD), they are one of the most preferred and favorable choices in detecting the recent SARS-CoV-2 [37]. LOD – the lowest detectable concentration of the analyte- is an important factor in evaluating the efficiency of the biosensor. Fig. 1 illustrates the operation of an immunosensor and a genosensor designed for detecting the viral surface proteins, whole viruses, and viral genomes, respectively. These strategies can be employed for detecting the novel coronavirus by modifying the surface of the sensor with virus-specific proteins or oligonucleotides.

As presented in TABLE I, in a recent study done by Chandra *et al.*, a tailored smart phone-assisted electrochemical impedance spectroscopy (EIS)-based biosensing system was designed for detecting COVID-19. The use of metal

TABLE I
RECENTLY DEVELOPED ELECTROCHEMICAL BIOSENSORS FOR RECOGNIZING COVID-19

Assay Structure	Target	Readout	Sample	LR	LOD	RT	Ref.
SPCE/NPs/nano-Dendroids/GO/Ab	S protein	Impedimetric	Clinical sample				[38]
SPE/carbon black nanomaterial/anti-mouse-IgG-MB/MAb anti-S or MAb anti-N/ PAb anti-S or PAb anti-N/PAb anti-rabbit-AP	S protein or N protein	Electrochemical	Saliva		19 and 8 × 10^{-9} g.ml^{-1}	30 mins	[43]
FTO/AuNPs/nCOVID-19 Ab	nCOVID-19 Ag	Potentiometric	Spiked saliva	10^{-15}-10^{-6}	10^{-14} M	10-30 s	[44]
SiO_2/Ti/AuNPs/Thiolated ssDNA	viral RNA, or c-DNA	Electrochemical (CMOS)	Spiked buffer and serum				[39]
SPCE/Au@SCX8-RGO-TB/CP/Au@Fe_3O_4/Probe	Viral RNA	Electrochemical	Clinical samples		200 copies/mL		[45]

LR: linear range, RT: response time, Ab: antibody, MB: methylene blue, IgG: immunoglobulin G, MAb: monoclonal antibody, PAb: polyclonal antibody, AP: Alkaline Phosphatase, NP: Nucleocapsid protein, FTO: fluorine-doped tin oxide electrode, SPE: screen-printed electrodes, SCX8-RGO: p-sulfocalix(8)arene functionalized graphene, TB: toluidine blue

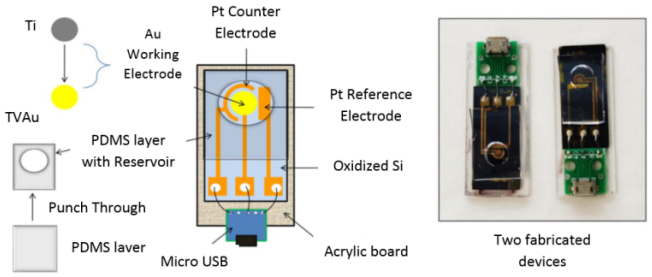

Fig. 2. A configuration of the compact electrochemical system presenting different constituents and a real image of the constructed devices [39].

nanoparticles (NPs), nano-dendroids, and graphene oxide (GO) nanocomposites for functionalizing the screen-printed carbon electrode (SPCE) provided an extraordinary electrical property and a large surface area for immobilizing a considerable amount of antibodies for capturing higher amounts of the biomarker. They also indicated the feasibility of redesigning this system for recognizing the recently found COVID-19 related markers [38]. Another smartphone-assisted DNA hybridization-based electrochemical genosensor was fabricated to detect the genetic material of the COVID-19. This system did not require complicated arrangements of data gathering from cumbersome electrochemical devices. Thus is an ideal candidate for POC detection (See Fig. 2) [39]. The use of electrochemical biosensors for detecting viral particles is not a recent topic [40]. It has been evolving since the last decades and numerous research studies are aiming at designing an efficient system for quantifying the amount of viral infection-related biomarkers in human biofluids [61]. According to TABLE II, in Hsu and coworkers' study, a scalable electrochemical Complementary metal-oxide semiconductor (CMOS)-based biosensor array was designed for detecting the Zika virus genome. This miniaturized on-chip sensor enables a mostly digitalized polar-mode measurement which boosts the SNR considerably. The operation principle of this structure is based on assessing the alterations resulted from DNA hybridization on the sensor's surface employing a trans-impedance enhancer, a detector, and a primary converter. This EIS-based biosensing system holds the potential for accurate and reliable biosensing in POC applications [47]. In another work (See Fig. 3), an economical paper-based sensor was proposed for identifying influenza virus H1N1 antigen in 30 minutes. The surface of the paper was amended with silica nanoparticles which increased the hydrophobicity. This is an imperative feature in designing paper-based biosensors. Besides, stencil-printed carbon electrodes were modified by single-walled carbon nanotubes and chitosan to enhance the preciseness of the sensor by amplifying the signal. In the final stage, the antibodies were immobilized using GA. The sensitivity of the designed system was evaluated by differential pulse voltammetry techniques. The results showed that this structure was able to recognize down to 113 PFU mL^{-1} of the viral particles in Phosphate-buffered saline (PBS) and saliva samples [49].

These examples verify the possibility of reusing the strategies employed in the recently designed biosensing systems for detecting COVID-19 related biomarkers. Although electrochemical biosensors have been thoroughly studied in lab-based arrangements, they are not fully commercialized thus far. Already established electrochemical genosensors like the ePlex platform by GenMark Diagnostics are comprised of PCR with microfluidic systems. It can rapidly identify not only SARS-CoV-2 but also other respiratory pathogens by its multiple nucleic-acid-modified gold electrodes [62]. Another marketable system was developed by Roche diagnostics to detect SARS-CoV-2 antibodies based on electrochemiluminescence technique. This methodology represents a similar selectivity with slightly lower sensitivity in comparison to ELISA [63]. However, at this time, there is not a commercially-available system using electrochemical biosensors with electrochemical readout techniques for spotting SARS-CoV-2-related antibodies. With the ever-increasing research work and growing knowledge regarding the novel coronavirus, an electrochemical-based SARS-CoV-2 diagnostic test can be developed and commercialized as an easily-available alternative. For example, immunosensors can be designed to exploit antibodies against the surface proteins of the novel coronavirus. Or in the same way, researchers can focus on fabricating geno or aptasensors for identifying the genetic material of the pandemic-causing virus.

B. Optical

The other category of rapid, and cost-effective biosensing systems are the optical biosensors [64]. They are composed of a target-specific BRE and an optical transduction unit for

TABLE II
RECENTLY DEVELOPED ELECTROCHEMICAL BIOSENSORS FOR RECOGNIZING OTHER VIRAL INFECTIONS

Application	Target	RE	Linker	Surface	Sensor	LOD	Sample	Ref.
AIV detection	Viral DNA	DNA	APTES GA	SiO_2	Impedimetric (On-chip)	1×10^{-15} M	Buffer	[46]
Zika Virus detection	Viral oligonucleotide	ssDNA		Al/Ni/Au	EIS (On-chip)		Buffer	[47]
EBV detection	viral oligonucleotide	DNA	PATP EtBr	Graphite	Electrochemical	17.32×10^{-9} M	Buffer	[48]
IV H1N1 detection	Whole virus	Ab	silica NPs SWCNT Chitosan GA	SPCE	DPV	113 PFU mL^{-1}	Saliva	[49]
WSSV detection	Whole virus	Ab	CB@Ses-Qn HRP	GCE	CV	9.9×10^{-7} M	Real samples	[50]
FLUAV detection	HA	Anti- H5N1	PANI-coated EAM NPs AuNPs Glycan	SPCE	Electrochemical - SPR	1.4×10^{-6} M	Buffer	[51]
DENV detection	NS1	DGV BP1	MUA EDC/NHS	GE	SWV, EIS	1.49×10^{-6} g/mL	Human plasma	[52]
MERS-CoV and HCoV detection	MERS-CoV protein	Ab	AuNPs	CE	SWV	1.0×10^{-12} $g.mL^{-1}$	Spiked nasal samples	[53]
swine virus H1N1 detection	HA	Anti-HA	His6-H1 HA MBT DPM-Cu	Gold	SWV		Diluted vaccinated mice sera	[54]
IV detection	M1 protein	anti-M1	PABA EDC/NHS	Boron doped diamond electrode	Electrochemical	1×10^{-15} g/ml	Saliva buffer	[55]
DENV-3 detection	DENV-3 sequences	DNA		PGE	DPV	3.09×10^{-9} M	Human serum	[56]
Dengue virus detection	Dengue toxin	Ab	CNT AuNP	GE	Electrochemical	3×10^{-13} g/mL	Human serum	[57]
Dengue virus detection	ss-31 mer DNA	59-aminated DNA probes	nanoporous alumina	platinum wire electrode	Electrochemical	9.55×10^{-12} M	genomic DNA derived from PCR	[58]
CHIGV detection	CHIGV DNA	Probe DNA	MoS_2 NSs MB	SPGEs	Electrochemical (voltammetric)	3.4×10^{-9} M	Serum sample	[59]
Dengue virus detection	Dengue virus gene 1	18-mer ssDNA		PGE	DPV	9.2×10^{-10} M	Buffer	[60]

RE: recognition element, AIV: avian influenza virus, APTES: (3-Aminopropyl)triethoxysilane, GA: glutaraldehyde, ssDNA: single stranded DNA, Al: aluminum, EBV: Epstein-Barr virus, SWCNT: single-walled carbon nanotubes, DPV: differential pulse voltammetry, WSSV: white spot syndrome virus, HRP: horseradish peroxidase, CB: carbon nanoblack, Ses-Qn: sesamol-quinone, GCE: glassy carbon electrode, CV: cyclic voltammetry, FLUAV: Influenza A virus, PANI: polyaniline, HA: Hemagglutinin, EAM: electrically active magnetic, DENV: Dengue virus, NS1: nonstructural 1 protein, MUA: 11-mercaptoundecanoic Acid, EDC: N-ethyl-N′-dimethyl aminopropyl carbodiimide, NHS: N-hydroxysuccinimide, GE: gold electrode, SWV: square wave voltammetry, MERS-COV: Middle East respiratory syndrome corona virus, HCoV: Human coronavirus NL63, AuNPs: gold nanoparticles, His6-H1 HA: His-tagged hemagglutinin, PABA: 4-aminobenzoic acid, MBT: 4-mercaptobutanol, DPM: thiol derivative of dipyrromethene, IV: influenza virus, DENV-3: dengue virus serotype 3, MB: magnetic bead, SPGE: screen printed gold electrodes, PGE: pencil graphite electrode, MoS_2 NSs: molybdenum disulphide nanosheets

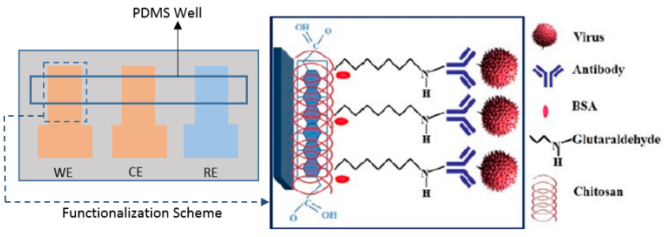

Fig. 3. The paper-based immunosensor, and the modification of the working electrode (Reconstructed from [49]).

producing a signal which is in proportion with the concentration of an analyte [65]. Their functionality in interdisciplinary methods has attracted great attention in recent years. Therefore, a large number of research studies have focused on this important technology during the last few decades [66]. Optical techniques offer more advantages in comparison to electrochemical ones since the detection of the target molecule is done with low energy consumption [67]. Besides, the high sampling speed, extraordinary LODs, real-time and multiplex assessment, simple fabrication process, small size, low reactant usage, and short response time make them one of the most preferred POC approaches [68]. In order to quantify the concentration of the target analyte in a precise manner, it is imperative to immobilize a great quantity of BREs on the sensor's surface [69]. The analyzed biomolecule which has a higher refractive index links to the immobilized BRE with a lower refractive index and causes a local change that is recordable by the transducer. It converts this variation to a quantifiable electric signal [68]. In general, optical platforms are classified into two subgroups of label-free and label-based. The first category exploits the direct interaction between the target and the transducer, whereas the latter employs a reporter for distinguishing the generation of a signal through

TABLE III
COMPARISON OF LABEL-BASED AND LABEL-FREE BIOSENING

Label-based biosensing		Label-free biosensing	
Advantages	Disadvantages	Advantages	Disadvantages
Multiplex quantification	Interference in coupling events	Simple, rapid, low-cost, low consumption of reagents, portable, possibility of detecting small biomolecules in their natural conformation in a multiplex manner	Inaccuracies due to environment

a fluorescent, luminescent, or colorimetric technique [70]. A variety of labels can be used for this purpose including, gold nanoparticles [71], upconversion nanoparticles [72], and quantum dots [73]. This tag is usually linked to one of the biological elements, however, it can sometimes influence the coupling event and cause some malfunctions in the system. A comparison of label-based and label-free biosensing is summarized in Table III. Generally, in comparison to electrochemical techniques, color-change-based methods are considered simple to read, since the result is observable without any intricate equipment. However, the tagging process is costly, laborious, and time-consuming. Additionally, a signal bias can occur as a result of the uncontrolled quantity of fluorophore labels on the biomolecules [74]. Though, they still display an acceptable performance and are very popular in the early detection of disease [75]. As summarized in TABLE IV, Chen *et al.* reported a swift lateral flow immunoassay (LFIA) based on lanthanide-doped polysterene nanoparticles (LNPs) for spotting produced IgG antibodies in human serum against SARV-CoV-2 in 10 minutes. In this order, the surface of the device was coated by a specific viral phosphoprotein to determine the presence of IgG in the sample. Additionally, IgG antibodies were marked by LNPs to be detectable. Since the obtained results were analogous to RT-PCR results, this approach can be used for early detection, monitoring the progression, and treatment of viral infections [76]. Another similar platform which can be seen in Fig. 4 was developed by Feng *et al.* who constructed an immunofluorescent assay for detecting SARS-CoV-2-specific IgM and IgG in human serum in less than 10 minutes. The viral nucleocapsid (N) protein acted as the probe of this system, where Lanthanide,

Fig. 4. Illustration of SARS-CoV-2 IgG/IgM chromatographic test and an actual image of human serum testing results under a UV lamp which shows a high concentration of IgM and IgG (Reconstructed from [77]).

Eu(III) fluorescent microsphere was employed as the reporter. The high sensitivity of this biosensing system enables its use in serodiagnostic applications [77]. The exploitation of optical biosensing platforms for virus detection can be seen in TABLE V. For instance, Donaldson and colleagues' introduced a speedy and accurate method to identify Variola virus (smallpox). This sandwich-type system used anti-Vaccinia antibodies labeled with cyanine 5 dye. The generated signal was sensed utilizing the Analyte 2000 biosensor which provided an excitation light by its laser diode. As a result of the fluorescent molecules' excitation and the emission of a portion of their energy into the waveguide, the target analyte was recognized. The LOD of the system was 2.5×10^5 pfu/ml in swab samples [78]. Fig. 5 presents an immunofluorescence biosensing microsystem for the detection of AIV based on ZnO nanorods. The structure and extraordinary attributions of these nanomaterials enhanced the sensing power of this device substantially.

In addition, this highly-selective microfluidic-based immunosensor facilitated multiplex detection of viral targets concurrently. Therefore, it is an appropriate candidate for a cheap and easy to use detection method [80]. By replacing the BRE of these successful systems with the target-specific biomolecules which are capable of detecting COVID-19 biomarkers, pioneering rapid tests can be developed.

The second group of optical biosensors -Label-free detection systems- provide a fast and easy-to-use method for biochemical and biological applications [66], [82], [83] including the identification of the viruses [84]. They not only necessitate minimum sample preparation steps but also facile and steadfast recognition. This attribution becomes essential in a pandemic situation since rapid management of the virus's transmission speed is of high importance [85]. Hence, these innovative devices are one of the appropriate choices for detecting COVID-19. For instance, Murugan *et al.* discussed the possibility of fabricating a handy plasmonic fiber-optic absorbance biosensor (P-FAB) system for detection of SARS-CoV-2' N protein in the saliva sample within 15 minutes. Based on their previous research works, this well-documented biosensor (Matrix/AuNPs/thiol-PEG-NHS/anti-N protein) has been successfully utilized for detecting different biomolecules such as proteinaceous antigens and endotoxins. It is noteworthy that, they attained LODs down to 10^{-18} M. Owing to the adaptability of this device, they believe it is feasible to redesign this system for identifying SARS-CoV-2' N protein in saliva samples with slight modifications in its matrix. This pioneering technology is very promising in the early detection and control of the current and future pandemics [87]. Over the past few decades, several optical sensing devices have been projected for virus detections [88]. As listed in TABLE VI, Nagy and colleagues proposed a CMOS-based immunosensor for multiplex detection of anti-HIV (human immunodeficiency virus) antibodies in serum samples exploiting metal nanoparticles as signal amplifiers. The LOD of the system was reported 10 μg/ml. Using a device based on CMOS technology offers numerous benefits including, facile large-scale production, high-throughput sensing, high sensitivity, and superior selectivity [89]. As can be seen in Fig. 6, a very recent study done by Janczuk-Richter *et al.*, an optical fiber-based immunosensor was reported for norovirus virus-like particles (VLPs) quantification. It could successfully spot 1 ng/mL of the target analyte in a short time (40 minutes).

This compact and low weight device can be utilized in detecting other types of viral particles as well as vaccine research [86]. The success of these investigations demonstrates their adaptability of being redesigned for identifying SARS-CoV-2.

TABLE IV
RECENTLY DEVELOPED LABEL-BASED OPTICAL BIOSENSORS FOR RECOGNIZING COVID-19

Assay Structure	Target	Readout	Sample	RT	Ref.
LFIA(nitrocellulose membrane/recombinant N protein of SARS-CoV-2/Mouse anti-human IgG antibody labeled with LNP)	IgG	Chromatography	Human serum	10 mins	[76]
Nitrocellulose membrane/NP conjugated fluorescent microsphere	IgM and IgG	Fluorescent	Human serum	10 mins	[77]

TABLE V
RECENTLY DEVELOPED LABEL-BASED OPTICAL BIOSENSORS FOR RECOGNIZING OTHER VIRAL INFECTIONS

Application	Target	RE	Linker	Surface	Sensor	LOD	Sample	Ref.
Vaccinia virus detection	Whole virus	Ab	Cyanine 5 dye		Fluorescent	2.5×10^5 pfu/ml	seeded throat culture swab specimens	[78]
SARS-CoV detection	N protein	RNA aptamer	QDs ProLinker™	Glass chip	Fluorescent (On-chip)	0.1×10^{-12} g mL^{-1}	Buffer	[79]
AIV detection	H5N2 AIV	mAb	GPTMS SH-PEG Biotin Cy3-SA	*ZnO nanorod*	Fluorescent	3.6×10^3 EID_{50} mL^{-1}	Buffer	[80]
HCV detection	HCV RNA	Nucleic acid probe	Thiol Citrate AuNPs cysteamine CTAB		Colorimetric/ spectrophoto metric	4.57 IU/µl	Clinical sample	[81]

QDs: quantum dots, PEG: polyethyleneglycol, HCV: Hepatitis C virus

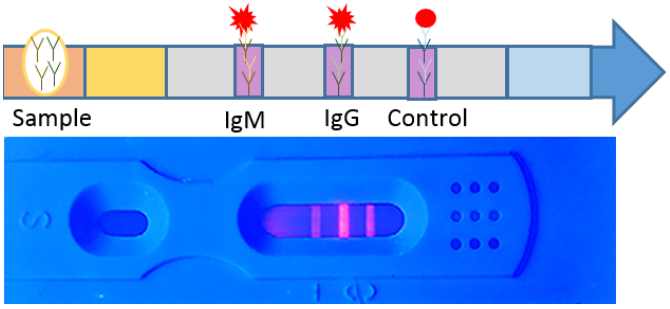

Fig. 4. Illustration of SARS-CoV-2 IgG/IgM chromatographic test and an actual image of human serum testing results under a UV lamp which shows a high concentration of IgM and IgG (Reconstructed from [77]).

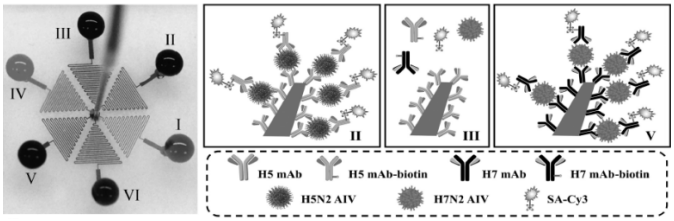

Fig. 5. Simultaneous identification of subtypes of AIV in one device. Microchannels II, III, and V that was modified with specific antibodies for AIV recognition [80].

C. Surface Plasmon Resonance (SPR)

The other well-established and frequently employed category of biosensors is the surface plasmon resonance-based devices [96]. These optical sensing systems which require no labeling operate based on the affinity interactions between an immobilized bioreceptor on the sensor's surface and the target biomolecule in the sample solution. After the occurrence of this bioreaction, the change in the refractive index is recorded and proportionated to the concentration of the analyte [97]. Due to their high accuracy and LODs down to picomolar levels, they have turned into one of the most powerful and trusted tools in examining the interrelationship between the biological particles [98]. For instance, they have been broadly utilized in detecting disease-specific biomarkers in diagnostic research studies. Like any other biosensing system, the main body of these structures comprises three subassemblies namely, the readout system, BRE, and delivery system [99]. A light wave in the optical readout platform of an SPR sensor stimulates a distinctive type of electromagnetic field which is called a surface plasmon. Because of its dissemination alongside a thin metal film, it can analyze the nearby environment. The binding of the target biomolecules to the BREs immobilized on the surface of the sensor increase the refractive index which accordingly alters the speed of the surface plasmon. This change can be assessed by the optical reader [97]. The employment of SPR-based biosensors for the early detection of viral infections has been highlighted in numerous research articles [100]. Their real-time, label-free, and noninvasive nature make them one of the suitable techniques for speedy and precise detection of coronavirus-related particles [101], [102]. As demonstrated in TABLE VII, Nag *et al.* discussed the possibility of using an evanescent wave absorbance (EWA)-based optical fibre and localized surface plasmon resonance (LSPR)-based sensor for swift recognition of SARS-CoV-2. Nanostructures such as AuNPs or polyaniline can be used as signal enhancers on the surface of the sensor prior to immobilizing specific antibodies (against the viral particles) or surface proteins of the virus which can sense the produced IgG or IgM in the patient's serum. The interaction between the probe and target alters the localized charge distribution, refractive index, and accordingly the light intensity and output signal [104]. Qiu and colleagues designed an LSPR-based biosensor implementing the plasmonic photothermal (PPT) effect for

TABLE VI
RECENTLY DEVELOPED LABEL-FREE OPTICAL BIOSENSORS FOR RECOGNIZING OTHER VIRAL INFECTIONS

Application	Target	RE	Linker	Surface	Sensor	LOD	Sample	Ref.
HIV detection	gp120 antigen , and mouse IgG	RAM Ab and anti-HIV		SU-8 AuNPs, silver	Optical (Off-chip)	10^{-5} g/mL	Rabbit Serum	[89]
Dengue virus detection	DENV-2 DNA	DNA	(APTS)-PSiNs	Plastic	Optical (Off-chip)	0.2×10^{-18} M	Saliva and urine	[90]
Ebola virus detection	Viral RNA	oligonucleotide	4FB- MBs		ARROW (On-chip)	0.021 pfu/mL	Clinical sample	[91]
VLP detection	main coat protein of the norovirus	Ab	TESPA APTES EDC-modified GFP	SiO_2	Optical (LPFG)	1×10^{-9} g/mL	Buffer	[86]
Dengue virus detection	Virus genome	DNA	AuNPs PSA succinimide	(poly(nBA-NAS)) microspheres	Optical	1×10^{-29} M	clinical samples	[92]
HIV detection	HIV-1 gp120	MLV	EDC	Gold	Optical		Buffer	[93]
Papillomavirus detection	VLPs	anti-VLP	APDMES GA	SiO_2	Optical (PhC)	1.4×10^{-9} M	10% serum	[94]
HCV detection	HCV NS5B	RNA aptamer	Streptavidin biotin	Octet platform	Optical	7×10^{-10} g mL^{-1}	Buffer solution	[95]

RAM: rabbit anti-mouse, DENV-2: dengue virus serotypes 2, PSiNs: porous silica nanospheres, linker: N,N'-bis-4-(hydroxysalicylidene)-phenylenediamine-nickel(II), 4FB: 4-formyl benzamide, ARROW: antiresonant reflecting optical waveguide, TESPA: 3-(Triethoxysilyl) propylsuccinicanhydride, GFP: Green fluorescent protein, LPFG: long-period fibre gratings, PSA: polyelectrolyte-coated poly(styrene-co-acrylic acid), BA: butyl acrylate, MLV: Murine leukemia virus, APDMES: 3-aminopropyldimethylethoxysilane, PhC: photonic crystal

TABLE VII
RECENTLY DEVELOPED SPR BIOSENSORS FOR RECOGNIZING COVID-19

Assay Structure	Target	Readout	Sample	LOD	RT	Ref.
Optical fibers/AuNPs or PANI/anti- IgG or anti-IgM	IgG or IgM	EWA- and LSPR	swab samples	100 units.ml^{-1}	1 hour	[104]
Complementary AuNI chip/Thiol-cDNA	SARS-CoV-2 sequences	PPT-LSPR		2.2×10^{-13} M		[103]

LSPR: localized surface plasmon resonance

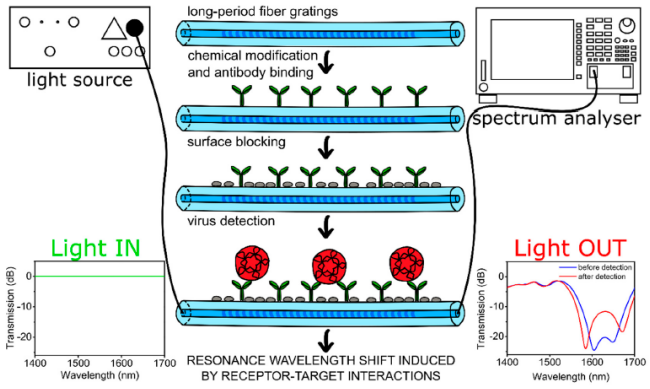

Fig. 6. Outline of the operation and surface functionalization for spotting norovirus [86].

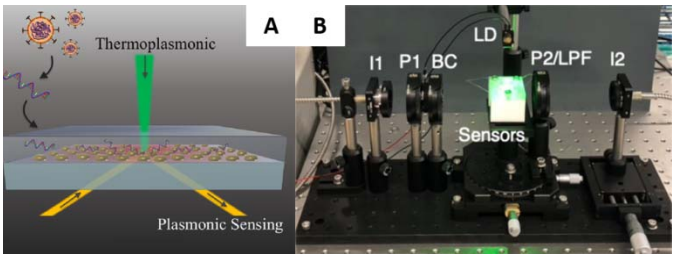

Fig. 7. A) Configuration of LSPR-based biosensor in combination with the PPT effect for COVID-19 identification, B) the setup of the biosensor [103].

detecting the SARS-CoV-2's genome (See Fig. 7). The DNA probes were modified by 2-D gold nanoislands (AuNIs) for ultra-sensitive detection. The employment of the localized PPT heat enabled precise differentiation of alike sequences. They reported a LOD 0.22 pM in a multiplexed sample. This successful research work shed light on the applicability of thermoplasmonic enhancement in viral disease detection [103]. SPR-based sensors are among the most sensitive systems for recognizing viruses (See TABLE VIII).

Besides, this technique is recently being used in plasmon-driven ultrafast photonic PCR and facilitates rapid detection of SARS-CoV-2 RNA. Currently, several studies have focused on designing portable devices for implementing PCR in around 15 minutes. This portable system incorporates reverse transcription, swift thermocycling, and on-site fluorescence-based recognition. The use of magneto-plasmonic photothermal nanoparticles speeds up the thermocycling process via plasmonic heating which decreases the required time and energy, significantly [105]–[107].

D. Field Effect Transistor (FET)

The next group of functional biosensing platforms is the field-effect transistor (FET)-based biosensors [110]. They are usually made from the unification of a BRE and an ion-sensitive field-effect transistor (ISFET) which is a popular form of electrical biosensors from the researchers'

TABLE VIII
RECENTLY DEVELOPED SPR BIOSENSORS FOR RECOGNIZING OTHER VIRAL INFECTIONS

Application	Target	RE	Linker	Surface	Sensor	LOD	Sample	Ref.
Influenza B virus detection	HA	Sialic acid	colloidal AuNPs		SPR	0.156 vol%	Buffer	[108]
SARS detection	Anti-SCVme	SCVme	GBPs EGFP	Glass/Gold-micropatterned chip	SPR	2×10^{-7} g.mL^{-1}	Buffer	[109]

SCVme: SARS coronaviral surface antigen, GBPs: gold binding polypeptides, EGFP: enhanced green fluorescent protein

TABLE IX
RECENTLY DEVELOPED FET BIOSENSORS FOR RECOGNIZING COVID-19

Assay Structure	Target	Readout	Sample	LR	LOD	RT	Ref.
Si/SiO_2/graphene/PBASE/anti-SARS-CoV-2	SARS-CoV-2	FET	Clinical sample		2.42×10^2 copies/ml		[121]
Graphene/CSAb	S1 protein	FET			0.2×10^{-12} M	2 mins	[118]
Silicon TFT/Al layer/aptamer	S protein	Electrical	Buffer sample (PBS)	10^{-14}-10^{-11}			[122]

PBASE: 1-pyrenebutanoic acid succinimidyl ester, CSAb: SARS-COV spike S1 subunit protein antibody, TFT: thin film transistor

TABLE X
RECENTLY DEVELOPED FET BIOSENSORS FOR RECOGNIZING OTHER VIRAL INFECTIONS

Application	Target	RE	Linker	Surface	Sensor	LOD	Sample	Ref.
IV diagnosis	GST-tagged-HA	CMP-NANA/ Biotin-tagged GST Ab	APTES GA Au-streptavidin	SiO_2/SiNW	FET (Off-chip)	1×10^{-15} M	Buffer	[123]
SARS diagnosis	N protein	AMPs	EDC/NHS/fibronectin	Si/ SiO_2/In_2O_3NWs	FET (off-chip)	10^{-7} M	Buffer	[124]
AIV H1N1 detection	synthetic viral antigen (H1N1)	anti-H1N1	APTES SBP	SiO_2-SiN-bottom SiO_2 ONO dielectric stack	ISFET		Buffer	[125]
Dengue Virus detection	RT-PCR product of DEN-2	PNA	APTES GA	Si/ SiO_2/SiNW	FET (Off-chip)	below 10^{-14} M	Buffer	[126]
JEV and AIV detection	JEV and AIV	Ab	carboxy Graphene EDC/NHS	SiO_2	FET	1×10^{-15}M and 10^{-14} M	Buffer	[127]

GST: glutathione S-transferase, AMP: Antibody mimic proteins, ONO: oxide-nitride-oxide, PNA: peptide nucleic acid, JEV: Japanese Encephalitis Virus

viewpoint [111]. A standard FET device is composed of a semiconductor channel that is interrelated to the source (S) and drain (D) electrodes. After the immobilization of BREs on this section, a potential is applied which controls the current flow between the S and D via the gate electrode. By measuring the varying conductivity of the channel which is dependent on the captured biomolecules, the concentration of the analyte is quantified [112]. In general, the charge transporters are electrons or holes. In the first circumstance, the device is categorized as an n-type, wherein the latter, is considered a p-type. If the target biomolecules are positively charged, we will have an accumulation of the electrons in an n-type system which causes an upward trend in the conductance. Reversely, this feature decreases as a result of electron depletion, if the captured species contain negative charges [113], [114]. The evolutions in the field of nanotechnology lead to the emergence of devices with higher performances and of course, FET biosensors are not an exception. The employment of nanostructures such as nanowires, nanorods, nanotubes, and metal nanoparticles provide a large specific area for immobilizing BREs [115]–[117]. Another important factor to consider is the type of transducer. Silicon nanowires, carbon nanotubes, and nanorods are among the most preferred alternatives because they offer high preciseness, physical stamina, high surface to volume ratio, chemical durability, superior conductivity, and scalability. They can be easily produced on a large scale which is a key parameter in designing a bioFET [119], [120]. Consequently, they have attracted the attention of scientists in the field of early disease detection. Especially, the recent pandemic situation triggered the need for a cheap and highly scalable device for the early detection of COVID-19 [15], [110]. Therefore, several studies have addressed this problem which is summarized in TABLE IX. A FET-based immunosensor was proposed by Seo and coworkers for the measurement of SARS-CoV-2 in biofluids. To increase the biocompatibility of the sensor's surface and functionalize it with desired antibodies, it was coated with sheets of graphene. This device could successfully detect 2.42×10^2 copies/ml of the whole virus in clinical samples. Because this biosensor requires no sample pretreatment or labeling, it holds the potential for being one of the alternative approaches in controlling viral infections [121]. As illustrated in Fig. 8, a similar Gr-FET –based immunosensing platform was developed by Zhang *et al.* which can recognize SARS-CoV-2'S S_1 protein in around 2 minutes with a LOD of 0.2 pM [118]. Thus it facilitates early diagnosis, monitoring, and decreasing the transmission rate of this infectious disease. A wide range of other viral infections has been monitored using FET-based biosensors

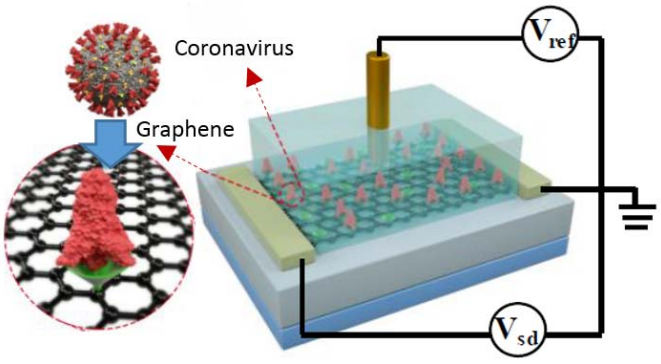

Fig. 8. Configuration of the FET-based biosensor modified with the graphene and S1 protein-specific antibodies (Reconstructed from [118].

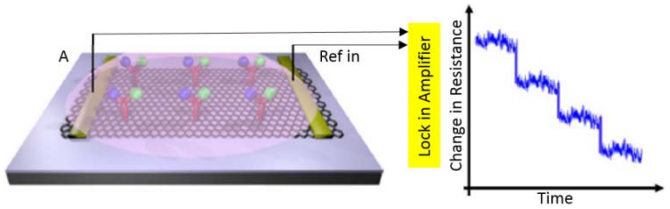

Fig. 9. Configuration of a FET-based immunosensor functionalized with graphene, EDC/NHS, and specific antibodies to target JEV and AIV and the resistance measurement for different concentrations of the target biomolecules using an amplifier (Reconstructed from [127]).

over the past few years. TABLE X depicts some of them. For instance, a CMOS-based silicon nanowire (SiNW) FET biosensor was established using Cytidine-50-monophospho-N-acetylneuraminic acid (CMP-NANA) as a specific receptor for the surface protein of the influenza virus. This methodology demonstrated high sensitivity, acceptable linear response, and desirable SNR which enable its large- scale production for being used in POC detection of viral infections [123]. Another miniaturized and straightforward FET-based immunosensing assay was fabricated for measuring JEV and AIV which was modified by carboxy functionalized graphene and target-specific antibodies (See Fig. 9). Real-time monitoring of changes in resistance showed the formation of the antibody-antigen complex. The accuracy, selectivity, simplicity, reproducibility, and probability of being integrated into standard FET-based devices specify the possibility of its mass-production for cheap and POC diagnosis of virus-related disorders [127].

III. Conclusion

Undoubtedly, the COVID-19 pandemic will be restrained in the immediate future. However, we should learn from this disastrous experience of the current century and be better prepared for upcoming hazards by adapting appropriate diagnostic interventions. Though, there is still a laborious way in front of the novel detection technologies. Currently, the dominant method of clinical detection is RT-PCR-based test kits. Although they are sensitive, selective, and well-established, they are time-consuming and necessitate costly instrumentation and experienced laboratory staff. These shortcomings underline a vital need for some rapid and user-friendly alternatives. POC biosensors can be one of the potent candidates. They provide rapid analysis, convenient use, affordable fabrication, multiplex detection, and facile mass production. The present review summarized the recently proposed biosensing platforms specialized to detect SARS-CoV-2-related biomarkers. Furthermore, it compared the core strategies of already designed biosensors for detecting other types of viruses and argued their potential to be used for identifying COVID-19. Especially, the significance of electrochemical, optical, SPR- and FET-based biosensors in the recognition of COVID-19 is underscored. They hold huge potential for being used as self-sufficient devices for COVID-19 identification in asymptomatic cases beyond laboratory settings, in houses, hospitals, airports, and even in remote areas. It is worth noting that the integration of microfluidic technology into the structure of biosensors facilitates the concurrent assessment of multiple biomarkers which increases the accuracy of the test. Besides, advances in bioengineering for designing unique BREs would enable highly-selective sensing platforms. Also, the employment of nanostructures decreases the background noise by boosting the available surface area. However, there are still challenges to be tackled to optimize the performance of these miniaturized devices. More examinations are required to ease the using procedure and uniting all the compartments into a single device at the lowest possible expense. Utilizing smartphones and particular apps that make analyzing the data and tracking the progress of the disease easier is another functional approach that should be improved in future studies. Also, removable power supplies like batteries can be added to the structure of biosensors to enhance their practicality specifically in places with restricted electricity sources. To conclude, considering that such pandemics are probable to reoccur, investing in attentiveness against these global threats is highly imperative. This cooperative and universal duty cannot be fulfilled without the collaboration of universities, companies, funding agents, and the government. We expect that well-timed screening based on robust biosensing strategies might relax severe quarantine and social distancing rules.

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