



New approach in SARS-CoV-2 surveillance using biosensor technology: a review

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Abstract

Biosensors are analytical tools that transform the bio-signal into an observable response. Biosensors are effective for early detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection because they target viral antigens to assess clinical development and provide information on the severity and critical trends of infection. The biosensors are capable of being on-site, fast, and extremely sensitive to the target viral antigen, opening the door for early detection of SARS-CoV-2. They can screen individuals in hospitals, airports, and other crowded locations. Microfluidics and nanotechnology are promising cornerstones for the development of biosensor-based techniques. Recently, due to high selectivity, simplicity, low cost, and reliability, the production of biosensor instruments have attracted considerable interest. This review article precisely provides the extensive scientific advancement and intensive look of basic principles and implementation of biosensors in SARS-CoV-2 surveillance, especially for human health. In this review, the importance of biosensors including Optical, Electrochemical, Piezoelectric, Microfluidic, Paper-based biosensors, Immunosensors, and Nano-Biosensors in the detection of SARS-CoV-2 has been underscored. Smartphone biosensors and calorimetric strips that target antibodies or antigens should be developed immediately to combat the rapidly spreading SARS-CoV-2. Wearable biosensors can constantly monitor patients, which is a highly desired feature of biosensors. Finally, we summarized the literature, outlined new approaches and future directions in diagnosing SARS-CoV-2 by biosensor-based techniques.

Keywords Biosensors · SARS-CoV-2 · Detection · Epidemiology · Techniques · Microfluidic

Abbreviations

AIV	Avian influenza virus	SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
A(H7N9)	Avian influenza virus subtype strains (low pathogenicity strains)	SARS	Severe acute respiratory syndrome
A(H5N1)	Avian influenza virus subtype strains (high pathogenicity strains)	MERS	Middle East respiratory syndrome
		HAdV	Human adenovirus
		WHO	World Health Organization
		PCR	Polymerase chain reaction
		RT-PCR	Real-time polymerase chain reaction

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NA	Nucleic acid
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
MIP	Molecularly imprinted polymer
LHBB	Luminescent hybridoma-based biosensor
PAFI	Plasmon-assisted fluoro-immunoassay
POC	Point-of-care
POF	Portable optical fiber
QCM	Quartz crystal microbalance
SH-SAW	Shear horizontal surface acoustic wave biosensor
SPR	Surface plasmon resonance
LSPR	Localized SPR
EBs	Electrochemical biosensors
OBs	Optical biosensors
PB	Piezoelectric biosensor
IS	Immunosensors
EZB	Enzymatic biosensors
GS	Genosensor
WCBs	Whole-cell biosensors
MFB	Microfluidic biosensors
HRPs	Horseradish peroxidases
PAN	Polyaniline
BOD	Biochemical oxygen demand
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats-associated protein 9
SERS	Surface-enhanced Raman scattering
PPT	Plasmonic photothermal
LOD	Limit of detection
LOC	Lab-on-chip
Pe	Péclet number
Re	Reynold's number
Ca	Capillary number
LAMP	Loop-mediated isothermal amplification
LFDA	Laminar flow-assisted dendritic amplification
MFC	Microbial fuel cell
NB	Nano-biosensors
MNPs	Metal nanoparticles
LFT	Lateral flow test
MHealth	Mobile health
IL-6	Interleukin 6 test
SAM	Self-assembled monolayers
CBC	Complete blood picture
ESR	Sedimentation rate
CRP	C-reactive protein
CT scan	Computerized tomography scan

Introduction

In the twenty-first century, many respiratory distress such as avian influenza (A(H7N9, H5N1)) and other critical acute respiratory syndromes, among others, have faced human-kind, and those have influenced human health and development progress (Narita et al. 2021; Zaidi 2021). At the end of 2019, new severe respiratory distress has spread in China, Wuhan city, and then transferred to the whole world (Nemudryi et al. 2020; Samson et al. 2020; Qiu et al. 2020). Since the World Health Organization (WHO) revealed that coronavirus-2 (SARS-CoV-2) has an etiological agent of the new coronavirus strain epidemic disease, great efforts have been made to discover a vaccine or limit its spread (Barcelo 2020). The spread of SARS-CoV-2 has infected millions of persons in over 213 countries (Suleman et al. 2021), which excited the confirmation of a higher and widespread case more than those that have been appeared since 2003 regarding a severe acute respiratory syndrome (SARS) and in 2012 regarding the middle east respiratory syndrome (MERS) (Wang and Anderson 2019; Wang et al. 2020). Thus, laboratory diagnosis for epidemic prevention and control has been considered one of the foremost priorities. Fast testing diagnosis (e.g., antibody/antigen testing and nucleic acid (NA)-based polymerase chain reaction (PCR) “real-time PCR (RT-PCR)”) has frequently been used and developed to cover the epidemic spread (Jin et al. 2020; Li et al. 2020).

In such difficult situations like COVID-19, when health-care facility professionals are seeking for smart and innovative treatments or selecting a certain type of device for their patients, biosensors play a vital and beneficial function. Biosensors give such chances to more easily and effectively address and handle the difficulties that have previously been raised as well as future concerns. These technologies can be used for illness diagnosis, positive environment providing, monitoring, defense-related toxins, food quality monitoring, prosthetic devices, and medical discoveries (Bahl et al. 2020a).

Additionally, biosensors may convenient to enable the acquisition of both pathogen information in a short time and host response information as well. This could facilitate the prevention process and quick diagnosis for such kinds of viruses as SARS-CoV-2 (Xu et al. 2020; Mao et al. 2020a; Ma et al. 2021). For instance, novel biosensors such as electrochemical biosensor (EB), optical biosensor (OB), and surface plasmon resonance (SPR) are used for the detection of RNA viruses as “clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR-Cas9)” based on a paper strip, nucleic acid-based, aptamer-based, and antigen-Au/Ag nanoparticles (Samson et al. 2020).

Biosensor might be very useful in order to identify and monitor the SARS-CoV-2 virus in the air. It swiftly

overcomes biological boundaries as well as technical restrictions. This technique aids in determining how long a virus may survive in the air when it is mostly transmitted from person to person. It is also useful for determining whether or not a condition is caused by an infection. It evaluates different laboratory tests and the cause of several infectious diseases in the air automatically (Bahl et al. 2020a).

Additionally, patients who are infected with SARS-CoV-2 have confirmed their viral ribonucleic acid (RNA) in feces (Barcelo 2020). Tetteh et al. (2020) reported that RNA of SARS-CoV-2 and COVID-19 has been detected in the sewage systems which are raising notable concerns about its pathogenic effects on wastewater systems. To date, there is no clear evidence towards SARS-CoV-2 survival in sewage systems or their fate to other ecosystems (WHO 2020); Langone et al. (2021) and other previous reviews revealed the SARS-CoV-2 detection in sewage systems and water environment (Singh et al. 2021). Moreover, the fate of human excreta could be extended to other ecosystems depending on the human pathogenic virus transmission through human body (e.g., mucus, saliva, feces, vomits, urine, and blood) or from a person to another, or indirect/direct contact of contaminated respiratory droplets, or viruses persistence on the surfaces like SARS-CoV-2 (Langone et al. 2021). However, few studies have overviewed this kind of viruses in sewage systems (Table 1), and biosensors gained great attention to be a promising tool for this epidemic.

Therefore, biosensors are miniaturized systems that have a high capacity for development to cover a wide range of usages even on-site (Ejeian et al. 2018; Maryam et al. 2021; Mohankumar et al. 2021). They provide a significant influence on transforming current analytical procedures into diagnostic strategies by restructuring their sensing strategies, improving traditional biosensors with nanotechnology and biotechnology, and detecting various viruses. There are universal applications in healthcare checking, metabolite

measurement, illness screening, insulin treatment, clinical psychotherapy, disease diagnosis, medication improvement, and SARS-CoV-2 disease detection (Bahl et al. 2020a). In this review, we summarized the literature, outlined new directions, and explored new approaches and methodologies for SARS-CoV-2 diagnosis and detection using biosensor-based techniques.

Biosensors advantages

Selectivity

It is the ability of the biosensor to detect the analyte exclusively. The structures of the viruses are relatively identical, and they have in some cases a nucleic acid genome, a genome-related protein capsid and lipid covering, and a protein layer (Weis et al. 1988). This protein coat helps to distinguish them from the bacteria (Green et al. 1982). Perhaps it can be possible that selective detection of the virus can occur by explicitly identifying and targeting certain capsid proteins with other proteins via protein-protein interactions (Rowe et al. 1999; Rossi et al. 2007; Nidzworski et al. 2014). Typically, adequate selectivity is accomplished by the optimum immobilization of the monolayer of the samples targeting the chosen biomarkers on the sensor surface (Formisano et al. 2015; Miodek et al. 2015). Nanotechnology developments and the speed at which material development and innovation progress give the researchers a solid opportunity to create chemical probes, which are only specific for the target being detected (Ge et al. 2014; Xi et al. 2020). Despite the apparent difficulty in designing specific probes, recent work revealed a probes' surface fouling issues which induced by the blended biomolecules through a network of conductive nanomaterial (Sabat  del R o et al. 2019). Also, after one month of exposure to unprocessed

Table 1 Biosensor-detected respiratory virus in wastewater

Year	Virus	Biosensor type	Reference
2020	COVID-19	POC	Mao et al. (2020a)
2016	Vibrio cholerae	LHBB	Zamani et al. (2016)
2015	Influenza A H1N1	PAFI	Lee et al. (2015)
2015	Bacteriophage MS2	MIP and SPR	Altintas et al. (2015)
2013	HAdV	POF	Yildirim et al. (2013)
2011	AIV	Impedance biosensor	Wang et al. (2011)
2009	Influenza A	Piezoelectric-based QCM sensors	Mao et al. (2009)
2009	Porcine Rotavirus	Photonic crystal biosensors	Pineda et al. (2009)
2008	Sin Nombre virus	SH-SAW	Bisoffi et al. (2008)

Abbreviations: AIV-avian influenza virus, COVID-19-coronavirus disease, HAdV-human adenovirus, LHBB-luminescent hybridoma-based biosensor, MIP-molecularly imprinted polymers, PAFI-plasmon-assisted fluoro-immunoassay, POC-point-of-care, POF-portable optical fiber, QCM-quartz crystal microbalance, SH-SAW-shear horizontal surface acoustic wave biosensor, SPR-surface plasmon resonance

human plasma, 88% of the initial interleukin 6 test (IL-6) detection signals were retained.

Sensitivity

The analyte adhesion on the sensor surface was determined either by the specificity, spacing, and affinity of biorecognition elements or self-assembled monolayers (SAM) (Chaki and Vijayamohan 2002; Zhou et al. 2006). The transducers (most commonly electric or optical) have also properties that affect the overall biosensor sensitivity (Sethi 1994). If SAM layer specificity is assured, even at a single molecular level, many tiny biomarkers (depths < 150 kDa) can be identified (Cannon et al. 2012; Wu et al. 2017). The development of the sensor is extremely important to be able to detect biomarkers attributed to pandemic strain, like SARS-CoV-2 in lower concentrations, preferring to the same molecule, and produce an output that can easily be read for the measured/needed concentration. Any such fundamental problems with the handling of biological liquids on sensor surfaces can also be resolved through additional methods, including sensor instruments using nanoparticles (Nam et al. 2003; Rasheed and Sandhyarani 2015) and microfluid detectors (Puleo and Wang 2009; Tekin et al. 2013).

Response time

In theory, most sensor transducers respond to the applied stimulus instantly (< 1 s), such as biomolecular contact with the surface of the sensor (Buerk 1995). However, all of these signals are sometimes necessary to post-process with advanced electrical and computer science systems. The sensor response time is vital for the pandemic to be actively used. For instance, temperature corrections (Hall et al. 2010) and the detection and elimination of background noise (Hall et al. 2013) will also contribute to a greater response time for the sensor. The architecture and function of signal conditional circuits are therefore important in order to ensure a rapid response time.

Multiplexing

When the characteristics of the viral strain are less widely understood at the early stages of the infection, the infection is frequently signed by the concentrations of common blood biomarkers. For example, in the case of SARS-CoV-2, some hematology and medical investigations such as complete blood picture (CBC), sedimentation rate (ESR), liver functions, C-reactive protein (CRP), and interleukins, in addition to computerized tomography (CT) scan on the chest are performed. A combination of more than two biomarkers is normally used to confirm this condition; therefore, it is an ideal multiplex system for the early detection of the disease

that enables multiple biomarkers to be identified. Multiplexing can be accomplished by physically isolating different areas of the sensor area where every isolated region works as a single sensor (Geißler et al. 2010; Li et al. 2018). Moreover, each area may be unique to a single type of biomarker (Varshney and Li 2009; Danilov et al. 2018; Mehta et al. 2018), in which a single transducer scans the isolated areas of the sensor surface, or the addition of several transducers connected to a single sensing area (Formisano et al. 2015; Tort et al. 2017) can be used to measure.

Disposable

SARS-CoV-2 as an example has a reproductive number that is higher than the calculated for SARS and H1N1, since the single-use sensors needed is between 1.5 and 2 to prevent contamination in sensing systems because pandemic viral strains are highly infectious. The most judicial method for designing a disposable sensor (Wang et al. 2013; Ramfos et al. 2014; Rose et al. 2014) is the modular approach.

Electrodes and readers should be constructed independently in this approach, where electrodes are made cost-effective. The use for immobilizing bio probes that are unique in the biomolecules of our interest could potentially become candidates for the creation of disposable electrodes by the use of glass (Zuo et al. 2013), paper (Ge et al. 2014; Desmet et al. 2016), plastic (Kröger and Turner 1997; Farsinezhad et al. 2013), metal (Solanki et al. 2011; Xiao et al. 2012), and ceramic or other material. These products have the best disposable features with paper-based biosensory electrodes (Zuo et al. 2013; Desmet et al. 2016) that have recently attracted public interest. Reading modules in the form of cell phone (Sun et al. 2016) can, on the contrary, deliver many benefits other than cost efficiency, including the frequent processing of data and access to integrated healthcare networks.

Life-time

The electrodes should also be simple to use and should last at least 1 month. Their simple use can encourage people to self-assess themselves and to make choices on their own self-isolation, essential and knowledgeable, to ensure the spread of disease can be minimized at its source (Gibson et al. 1992; Hannah et al. 2020). This allows for the creation of a variable degree of self-test and self-isolation.

Cost-effect

Intuitively, the reduced the cost of the biosensor, the much more efficient the system is. The biosensor's cost-effectiveness is expressed in its affordability (Han et al. 2020). In order to maintain the cost lower, so all people in the society

can tolerate it through disease outbreaks, the biosensor system can even be basically split into 2 parts: its first portion would be a removable electrode, such as a screen-printed electrode or a paper-based electrode, which could potentially be sold in retail pharmacy stores (Yoo and Lee 2010; Choi 2020). The electrode can have direct contact with body fluid. The second component of the sensor device could be a cell phone app that can effectively be used to read signals directly from the sensor (Broeders et al. 2013; Huang et al. 2018). Such applications may theoretically be made available to the government or health authority of the affected area or population.

On the other hand, an autonomous read-only device may even be built for data loggers that can be fitted in hospitals or on a country's border control posts for disposable sensors (J et al. 2018). There are definitely several biosensors available in supermarkets, such as paternity checks and side flow strips for sexually transmitting and for disorders already readily accessible. In addition, this will reduce the pressure on public health officials to diagnose the disease in a large population and may also contribute to prompt monitoring of the transmission of the disease.

Mass manufacturable

During pandemics, there is a pressing and high need for sensors that can specifically and easily diagnose the rapidly spreading outbreak. In SARS-CoV-2, the research rate is limited following the overall population due to an inability to have and meet several sensors and even in countries with the leading public health infrastructures (Dyer 2020; Gaur et al. 2020). In an optimal scenario, the population of a particular geographic area is equivalent to the number of biosensors being studied to ensure that all future communal participants are eligible to participate. While mass production sensors face an important technical challenge, recent production advances, for example, 3D printing (Manzanares Palenzuela and Pumera 2018) and machine molding [158], will lead in a very short space of time to the creation of a large number.

Autonomy and connectivity

Autonomy in the biosensing process ensures a high degree of reliability between electrodes and reading modules. The pandemic sensor measurement systems should be able, in addition to autonomy, to connect to the central hospital database to capture measurement data in real time. For instance, cellular devices collecting sensor data can be combined with a two-way communication channel to (i) pass data to the central database and (ii) immediately provide therapeutic

intervention or facilitate a situation for paramedical staff sent (Cortez et al. 2014; Roda et al. 2016; Wood et al. 2019).

Additional details regarding the responsiveness of a sensor can also be stored and troubleshot by networked healthcare providers. In addition, the central databases could easily be logged on to the venue, positive sickness cases, and personal information, including age, gender, and contact numbers. That will offer real-time intelligence to the government and healthcare policymakers to rapidly and reliably assess appropriate steps, including closing certain areas to avoid and reduce the rapid spread of the epidemic (Ferretti et al. 2020) (Fig. 1).

New approach in SARS-CoV-2 surveillance using biosensor technology

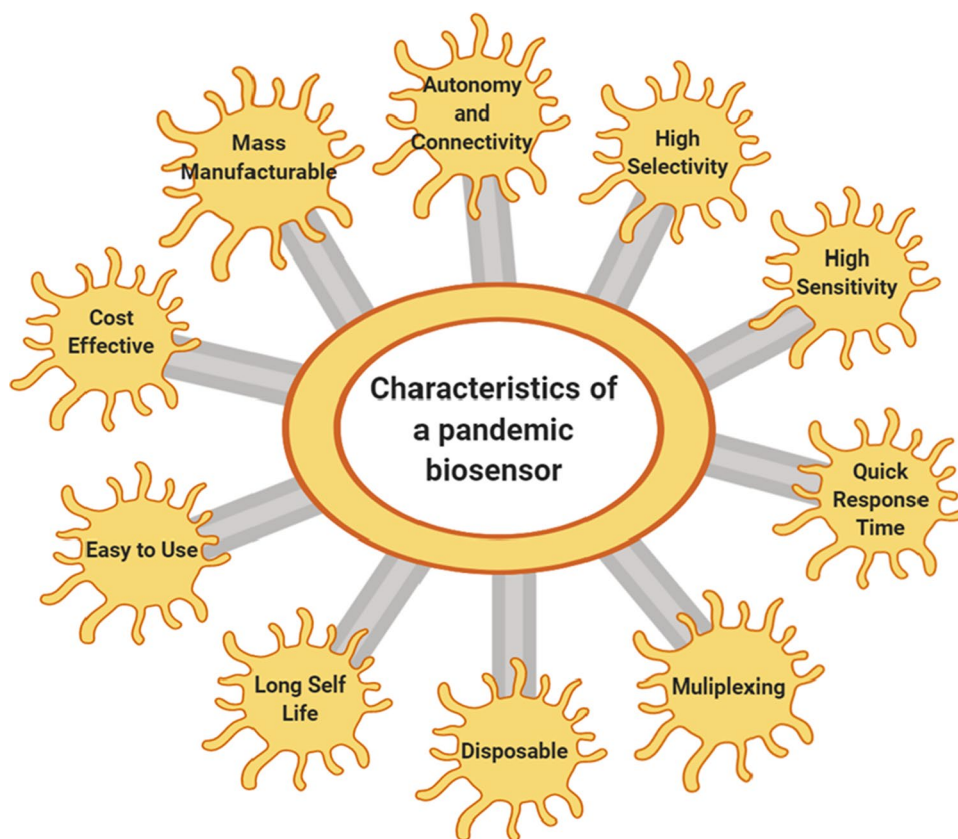
Electrochemical biosensors

Electrochemical biosensors (EBs) are a class of biosensors that use an electrochemical transducer to detect biological materials (Osman et al. 2019). EBs were found very effective tools beyond their potential capability to provide a specific quantitative or semi-quantitative analytical information, especially for organic materials; however, many EBs have yet been a widespread success (Riberio et al. 2020). EBs observe the distribution changes over the transducer surface, depending on the potentiometric, amperometric, or impedimetric transduction principles (e.g., enzymes, specific ligands, whole cells, and tissues). Meanwhile, the electrochemical biosensor works on transducing the biochemical events to electrical signals depending on the electrode component as solid support for the immobilization of the biomolecules and electron movement (Cho et al. 2020b).

Accordingly, there are many usages for EB; one of them is detecting the organic pollutants in wastewater through a wide range of biorecognition methods that influence biosensor performance (Ejeian et al. 2018). Notably, the amperometric transduction mechanism based on horseradish baroreceptor was employed, and a modified platinum electrode has also been accomplished by electrostatic attachment of horseradish peroxidases (HRPs) on polyaniline (PAN) (Nomngongo et al. 2012). This implies that a series of innovations for in situ wastewater monitoring concerns pollutants such biochemical oxygen demand (BOD) in very short time per minute with a high detection limit which has been existed or those capable for non-aerated conditions with high detection efficiency (Verma and Singh 2013; Yamashita et al. 2016).

Moreover, due to the recent events of outbreaks concerning the SARS-CoV-2 epidemic since 2019 and others in the last decade, the focus is directed into biosensors as a first crucial step due to their rapid and accurate diagnosis of infected cases (Mao et al. 2020b; Imran et al. 2021).

Fig. 1 Characteristics of an optimal biosensor for successful pandemic usage



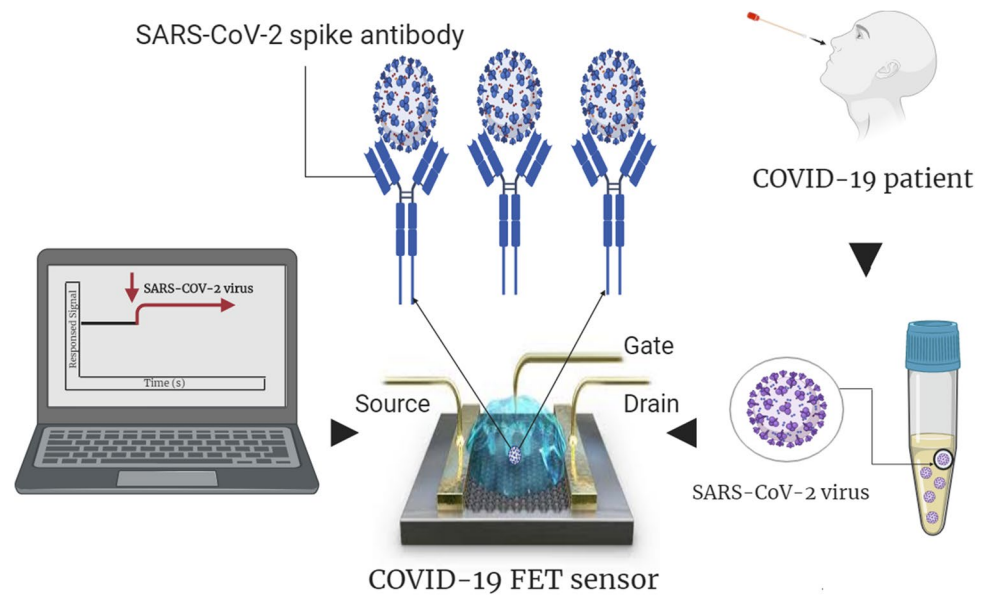
Furthermore, the early stages of SARS-CoV-2 monitoring in wastewater using biosensors could be a likely diagnosis in the current pandemic. Therefore, EBs have a wide application in detecting pathogens, besides the smart option concerning separating electrodes and readout on smartphones (Bhalla et al. 2020; Vidic and Manzano 2021). Because EBs have many advantages (e.g., miniaturization, mass manufacturing, and low cost), they are now becoming widely available in portable formats due to their commercial prices. Thus, the development process to upgrade their use in different fields is running constructively to cover many technologies such as non-labeling techniques which include surface-enhanced Raman scattering (SERS) and quartz-crystal microbalance (QCM) technologies for viral samples or others used for the detection of RNA viruses, such as influenza A/B, SARS-Corona, Ebola, MERS, Zika, and dengue (Loncaric et al. 2012; Han et al. 2016). Moreover, EBs are widely accustomed to detect nucleic acids, proteins, small molecular antibodies, and viruses as noted recently by Barcelo (2020). Besides, EBs have been used many years ago in the detection and diagnosis of viral infections. Due to their low cost, high selectivity and sensitivity (Seshadri et al. 2020), they have been used to detect different influenza A subtypes (H_1N_1 , H_5N_1) by using microfluid sensors. Also carbon electrodes sensors have been used to detect MERS and SARS.

For SARS-CoV-2, scientists are using similar techniques as those used to detect SARS infections. A coated transistor (Fig. 2) contains graphene sheets in the presence of SARS-CoV-2 antibodies to produce the desired sensor identification. As well, in another latest research, Mahari et al. (2020) designed three-electrode electrochemical sensors with the presence of carbon electrodes that are able to detect the SARS-CoV-2 viral infection within a limit of 120 fM in buffer solvent, which shows an additional advantage of electronic biosensors ability to detect viral infection at low concentration (Bhalla et al. 2020). Moreover, EB was developed for SARS-CoV-2 via detection of S and N proteins as reported by (Kudr et al. 2021).

Optical biosensors

There is a large number of biosensors that are based on the plasmonic principle, especially where transduction principles use optical components, for instance, photonic crystals (Rodriguez et al. 2019), waveguides (Ligler et al. 2002), lasers (Ma and Oulton 2019), and fiber optics (Socorro-Leránoz et al. 2019) are classified into optical sensors which are defined as compact analytical tools containing biorecognition sensing element integrated with an optical transducer system (Damborsky et al. 2016). As known, the primary target of the optical biosensor (OB) is to produce a signal

Fig. 2 Application of carbon electrodes sensors in COVID-19 detection



which is commensurable with the concentration of a measured substance (analyte). OB such as localized SPR (LSPR) and SPR were commercially available since the early 1990s (Cooper 2002), and they are used for the detection of viral strains of SARS (Huang et al. 2009), H1N1 (Kamikawa et al. 2012), influenzas (Takemura et al. 2017), and MERS (Lu et al. 2013). Chen and Wang (2020) have described the recent advancement in OB and focused on the mainstream of research in the biosensor, i.e., SPR, optical resonator-based biosensor, photonic crystal-based biosensor, optical waveguide-based biosensor, and optical fiber-based biosensor. Those biosensors have a history of epidemic diagnosis detection usage such as Ebola, HIV, and norovirus. This implies their potential ability to be used in nano-scale biosensors for virus detection and single virus imaging (Bhalla et al. 2020).

There are many advantages of the developed plasmonic techniques such as selectivity, short response time, and high sensitivity for the viral strains. However, there are major drawbacks such as high cost and complicated instrumentation being used for plasmonic system development which makes it difficult to use plasmonic techniques in point-of-care (POC) applications so difficult (Suleman et al. 2021). Therefore, the usage of these sensors remains incomprehensible for self-testing and mass production (Sheta et al. 2019b, 2019a).

The wide applications of the OB have extended to several biological materials which have approved high performance and sensitivity without complexity pretreatment in the detection of the biological system (Damborsky et al. 2016). In addition, they present meaningful progress towards food process control, drug discovery, clinical diagnostics, and even environmental monitoring, which has a desire of combining

the detection and imaging to provide a deeper understanding of pathogens and in biological samples as well (Maddali et al. 2020). This feature is allowing pathogen-specific tracers beyond the abnormalities in pathways that concern the disease at the molecular stage. In this regard, the dense biological tissues have a high absorbance potential rate that reduce the light intensity caused a subsequent decrease of the signal-to-noise ratio. This implies the need for advanced tools based on detection and imaging which thoroughly affect the field of OB to be applied in the further testing mechanism of viral pathogens. As mentioned in the previous part, that biosensors have been applied to detect pollutant levels on wastewater sufficiently and used to observe organic matter based on the immunoanalytical methods, which are known as fluorimetry for signal transducing in OB of organic pollutants (Ejeian et al. 2018), in addition to its common use for other pollutant monitoring in the environment such as antibiotics, hormones, and pesticides.

For the recent SARS-CoV-2 epidemic, OBs have been used in various ways, which present an alternative way for virus detection because of their cost-effective, safe, and not requires a nucleic acid amplification. Pashchenko et al. (2018) concluded that OB-based detection of infectious diseases can be used as POC diagnostic tools having many advantages noted in the previous section. Recently, a deep and great effort has been excited to find a sample tool for detecting viruses such as SARS-CoV-2 or others. For example, Samson et al. (2020) have developed an optical biosensor to detect the virus safely and reliably that combines two different biosensors, one is an optical and another one is thermal. As known, the sensor theory depends on a single RNA strand of the virus detection, in which the receptors are therefore representing the complementary sequences

that can reliably identify the virus. Moreover, a result in the probability of viruses spreading into wastewater could pose a serious effect on human health. OB has proved their potential ability to detect viruses in wastewater.

A novel biosensor was developed by Qiu et al. to accurately diagnose SARS-CoV-2 where LSPR and plasmonic photothermal (PPT) effects are combined as transduction principles in the sensing scheme (Qiu et al. 2020). Essentially, the DNA receptors are used for the detection of particular SARS-CoV-2 sequences through nucleic acid hybridization. With the compulsory use of nanoparticles and light in LSPR sensing, well-known thermoplasmonic at the plasmonic resonance frequency is being generated. According to the authors, this thermoplasmonic heat increases the in situ hybridization temperature that assists in the accurate distinction of two similar gene sequences. Besides, the LSPR biosensor shows excellent SARS-CoV-2 sequence selectivity with a lower limit of detection (LOD) at a concentration of 0.22 pM (Fig. 3).

Piezoelectric biosensor

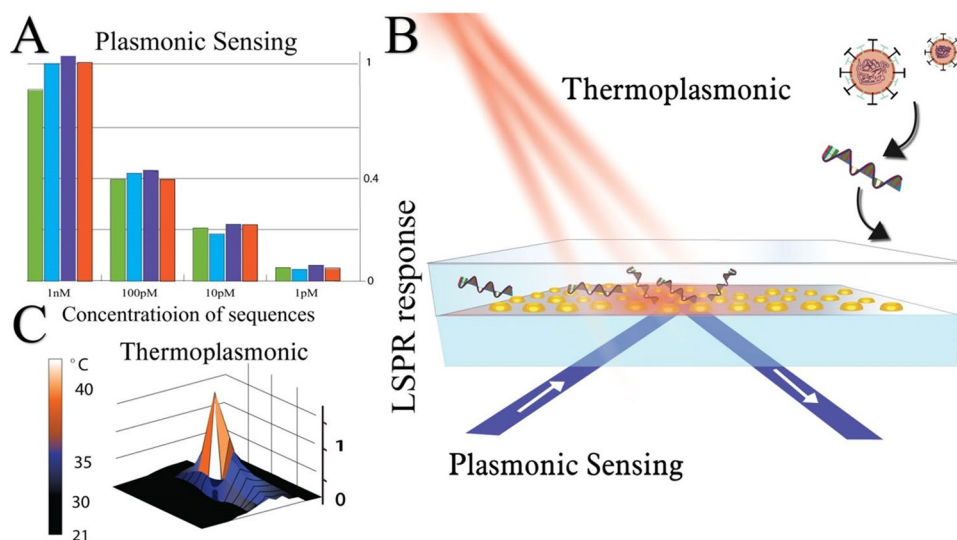
Piezoelectric biosensor (PB) utilizes the piezoelectric effect based on a physical phenomenon of material voltage production upon mechanical stress. This phenomenon can be reversed, and the mechanical stress can be produced upon giving voltage piezoelectric material surface (Narita et al. 2021). In PB, there is a proportional relationship between mechanical stress and the output electric charge. Moreover, fluid pressure is transmitted to a transduction element via pressure sensor diaphragm; hence, there is an additional proportional relationship between the force transmitted and transduction element which is once more converted to proportional electric charge. Piezoelectric effect can be seen in various materials such as anisotropic crystals (crystals

without a center of symmetry), quartz, aluminum phosphate, zinc oxide, aluminum nitride, crystalized topaz, lead, barium titanate, gallium orthophosphate, tartrate tetrahydrate, polyvinylidene fluoride, and polylactic acids (Pohanka 2018). In previously mentioned biosensors, transduction and sensing elements can be distinguished, unlike in PB since they are one and the same (Gautschi 2002). PB is widely used in the immunology field to determine numerous macromolecular compounds such as DNA (Kirimli et al. 2014), albuminuria (Muratsugu et al. 2002), and microorganisms such as dengue virus (Chen et al. 2009), and finally for the detection of SARS-C V-2 (Narita et al. 2021).

Immunosensors

Immunosensors (IS) are biosensor types in which they defined as a combination between a transducer and a biological recognition mechanism. This leads to a generation of a detectable signal associated with the changes in the biomolecule concentrations. There are two main components for this mechanism to occur, the ligand and analyte. The former is covalently immobilized to the matrix, and the latter is passed over the sensor in solution. In IS, the ligands refer to the antibodies, and this technology was first used in the mid-1990s for food analysis. Recently, there are many compelling progresses in IS miniaturization. Therefore, portable IS are commercially available enabling on-site and/or simultaneous detection of numerous biomolecules (Dupont 2011). IS have two major categories according to the principle, labeled and non-labeled IS. The design of labeled IS allows the immunochemical complexation (i.e., antigen-antibody complex) to occur on the sensor matrix surface. The immunocomplex formation on the matrix surface has many variations. Therefore, to be able to measure it via optical, potentiometric, and

Fig. 3 **A** Concentrations of various viral oligos measured using the dual-functional LSPR biosensors, **B** SPR mechanism, and **C** mapping the temperature distribution around the converted PPT heat source.



amperometric measurements, the label must incorporate into the immunocomplex in the last step (Fig. 4A).

Unlike labeled IS, the design of non-labeled IS allows the direct determination of immunochemical complexation through measuring the physical changes induced by the formation of the complex. There were many proposed IS as schematically illustrated in Fig. 4B. Solid matrix has either antigen or antibody immobilized on the surface for sensing device formation. In this case, higher sensitivity is required in the solid matrix to detect the immunocomplex formation. Several surfaces can be used to create non-labeled IS (e.g., piezoelectric material, electrode, optically active material, or membrane) (Aizawa 1994). The determination of the antibody or antigen starts by dissolving them in a solution to react with a complementary matrix-bound antibody or antigen for immunocomplex formation. This alternates the surface (e.g., intrinsic piezo-frequency, electrode potential, transmembrane potential) physical properties.

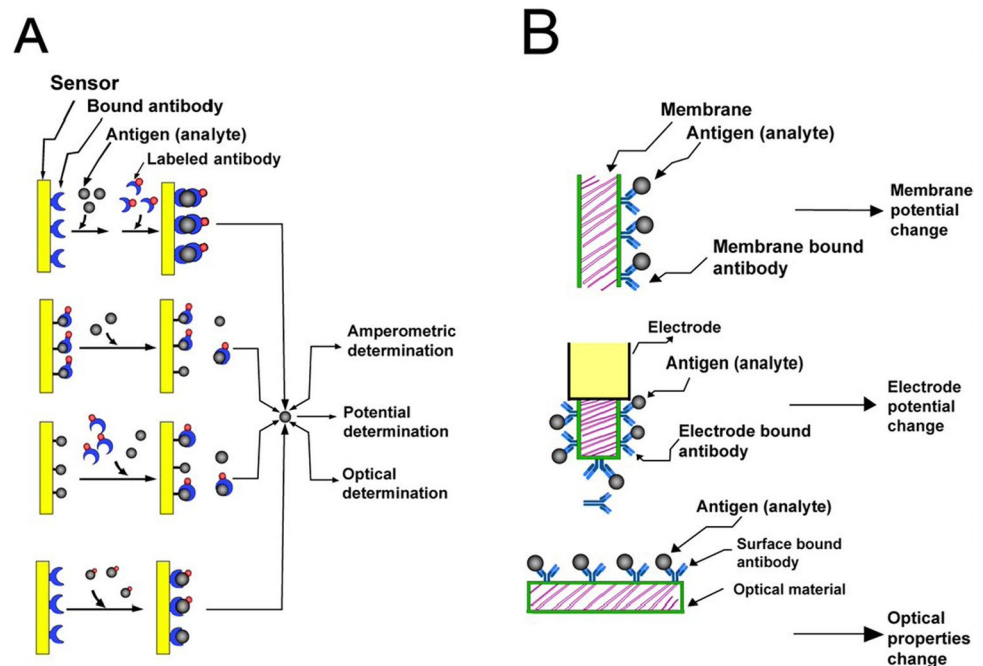
Microfluidic biosensor

Microfluidic technology became popular in the early 1990s (Manz et al. 1990; Harrison et al. 1992) for chemical separation applications. The technology simplifies fluids' small volume operations in the range of 10^{-6} to 10^{-18} l (μL –aL) (Mark et al. 2010; Choi et al. 2012; Puigmartí-Luis 2014). The implementation of microfluidics often utilizes planar substrates bearing enclosed channels with approximate widths, lengths, and depths of 100 μm , 10 mm, and 10 μm scales, respectively. Currently, microfluidic applications have been extended to include synthesis (Baxendale

et al. 2006; Baek et al. 2011), genomics (Wu et al. 2014), mazes (Fuerstman et al. 2003; Qin and Wheeler 2007), and music (Tan et al. 2014). The microfluidic community has an integrated lab-on-chip (LOC) system. It is considered a predominantly attractive vision that will reproduce laboratory-scale processes with lower cost, less time, and considerably smaller footprints than their conventional counterparts (Manz et al. 1992). A major difference between microfluidics and conventional systems is that the former depends on fluidic phenomena that show the importance of diffusion, viscosity, and surface tensions. These properties are frequently represented as dimensionless parameters including Péclet number ($Pe=vL/D$), Reynold's number ($Re=\rho vL/\mu$), and capillary number ($Ca, v\mu/\gamma$) where v is the mean fluid velocity, L is a characteristic length in the system, D is coefficient of diffusion, ρ is the fluid density, μ is dynamic fluid viscosity, and γ is surface tension. Generally, Pe , Re , and Ca values for microfluidic systems are low, which means, viscous forces dominate inertial forces (resulting in laminar flow), interfacial forces dominate viscous forces, and diffusion dominates convection. It is crucial to consider these phenomena when designing microfluidic systems for biosensors and electrochemistry. This phenomenon at micron length dimensions has been described in detail in previously published books (Tabeling and Chen 2005; Kirby 2010) and reviews (Beebe et al. 2002; Squires and Quake 2005). Examples of microfluidic biosensors (MFB) are displayed in Fig. 5.

Sun et al. have developed a smartphone-based multiplexing nucleic acid detection system integrating a silicon microfluidic chip for loop-mediated isothermal amplification

Fig. 4 **A** Labeled immunosensors and **B** non-labeled immunosensors



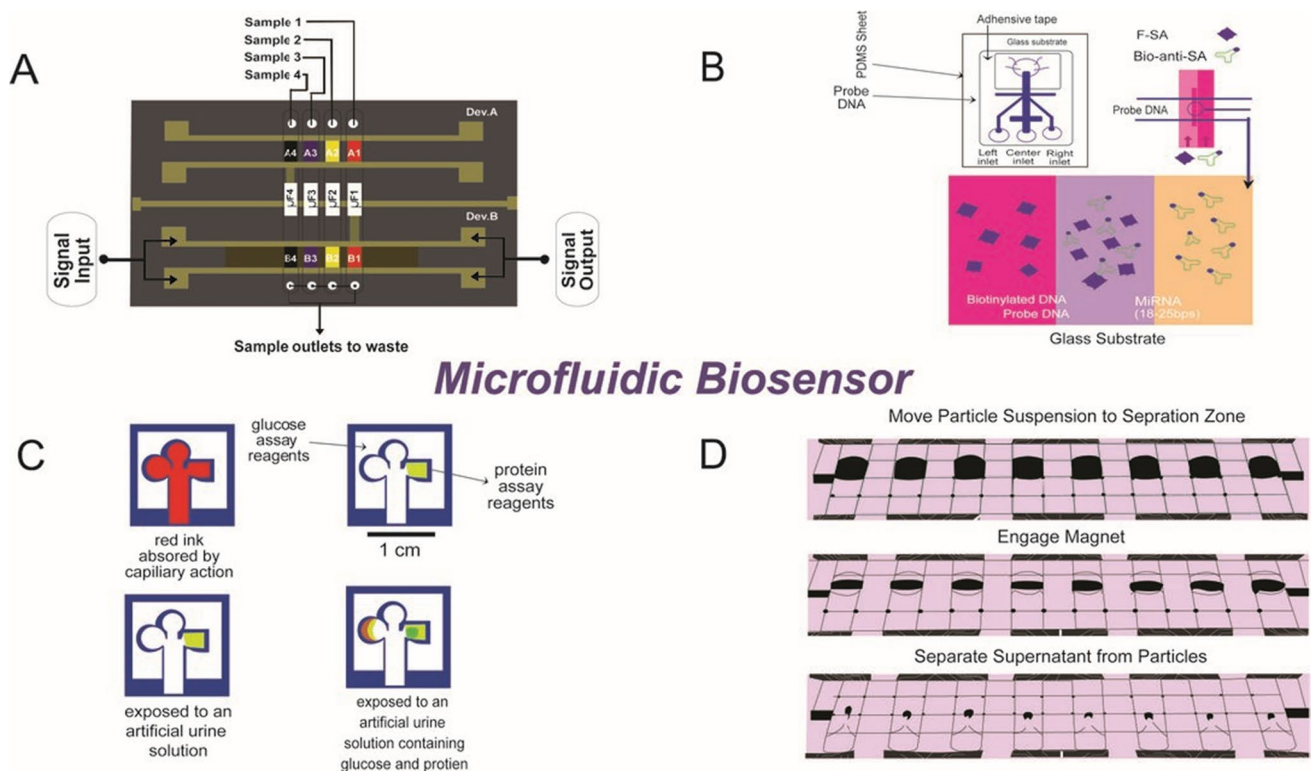


Fig. 5 Microfluidic biosensors. **A** Surface acoustic wave (SAW) biosensor, **B** lamellar flow biosensor, **C** paper-based biosensing, and **D** digital microfluidic-based biosensing

(LAMP) and a smartphone for fluorescence signal detection (Sun et al. 2020). No nucleic acid extraction step was realized on the microfluidic chip, and repeated manual pipetting was required during the assay. Also, Spindiag GmbH (Zengerle and Grötzinger 2020) company is currently developing a centrifugal microfluidic device for SARS-CoV-2 detection due to its short turnaround time. In centrifugal microfluidic biosensors, solutions are transported inside microchannels by spinning-induced centrifugal forces (Gorkin et al. 2010; Kong et al. 2015). Centrifugal microfluidics uses a motor capable of rotating the chips at various speeds, which enables the multi-step mixing of the solution. Therefore, the system has proven its efficacy in multi-nucleic acid testing. A portable centrifugal microfluidic system was developed for H3N2 virus detection (Stumpf et al. 2015).

Mitsakakis and Gizeli developed a surface acoustic wave (SAW) biosensor to apply microfluidic biosensing in microchannels (Mitsakakis and Gizeli 2011). SAW contains dual microfluidic channels and electrical contacts for signal input and output. It is possible to detect four different samples per sensor. Arata et al. developed biosensing in microchannels and lamellar flow-assisted dendritic amplification (LFDA) mechanism (Arata et al. 2012). The biosensor was developed by streptavidin-biotin dendrimer complex that is formed by probe-micro-RNA-biotinylated DNA sandwich.

The lamellar flow permits the continual addition of biotinylated anti-streptavidin antibodies (green) and fluorescent streptavidin (violet). Martinez et al. developed paper-based biosensing to determine protein and glucose by utilizing two regions. Liquid flow is directed by the hydrophobic patterning via capillary action (Martinez et al. 2007). Finally, Choi et al. reported an application of digital microfluidic-based biosensing showing the separation of the supernatant from magnetic particles by a permanent magnet. It is possible to implement large DMF electrodes and process multiple samples (Choi et al. 2012).

Nano-biosensors

As known, the nano-biosensors (NB) have a fundamental potential for the future of many diseases' diagnoses. Besides, it collaborates with nowadays technologies to take the diagnosis procedure to a new level (Shirvalilou et al. 2021). Generally, the NB is responsible for detecting biological agents such as antibodies, nucleic acid, pathogens, and other metabolites in the human body. The basic principle of the NB role is based on the affinity of the receptors to binding into the targeting bio-analytes, which in turn modulates the physiochemical signal associated with the binding. Then the transducer has the ability to capture and convert the

physiochemical signal into an electric signal. The variation in this signal could be measured and monitored, followed by analysis depending on different parameters like current, electric potential, conductance, impedance, mass, temperature, viscosity, and electromagnetic radiation leading to the identification of the presence or absence of the biological agent (Bahl et al. 2020b) (Fig. 6).

Recently NBs are used in the detection of the SARS-CoV-2 throughout the viral antigen detection or antibodies detection. For example, graphene is used for that purpose due to the electrical characters with negative charges; also, dendritic nanochips are used as nanomedicine in the determination of H_2O_2 in the blood. Metal nanoparticles (MNPs) like gold nanoparticles are also used as they have a potential electric property, excellent biocompatibility, and catalytic properties. The Chinese scientists and researchers developed nanoparticles based on diagnostic kits for rapid testing of SARS-CoV-2. These kits contain 2D materials, graphene, gold nanoparticles AuNPs, and carbon (Antiochia 2020).

Paper-based biosensors

Paper-based method for detecting SARS-CoV-2 counts as one of the lateral flow tests (LFT), also known as POC, like a pregnancy test. These tests have a similar principle of work as immunoassay technology (Antiochia 2021). The high demand for the POC tests is due to the low cost of the test, ease of use, rapid onset, biodegradability, and proper accuracy (Samson et al. 2020) (Fig. 7).

For SARS-CoV-2 the LFT was designed to detect the presence of human antibodies IgG and IgM in the patient blood sample. The test strip consists of the following: (i) sample pad, (ii) conjugate pad which has the SARS-CoV-2 antigen conjugated with nanoparticles (as gold), (iii) nitrocellulose membrane with control line coated with IgG and test line coated with IgM, and (iv) another absorbent pad

to absorb the excess sample. Adding the sample will flow along the test device, passing through the conjugate pad, which acts as the first stage if the target antigen is present. It will bind with the stored antibodies IgG forming a colored complex. Then the fluid passes to the nitrocellulose membrane in the second stage, forming a more density color line if the target antigen is present in the sample by binding with IgM antibodies. Finally, the sample reaches out to the absorbent pad, which is the last stage of the test, when the pad will absorb the excess sample amount. The result could be detected as acute infection in the case of a positive (colored) IgM and negative IgG or positive at both lines. In contrast, a positive IgG with a negative IgM indicates a later stage of infection (Choi 2020).

Mobile health (MHealth)

Mobile health biosensors have a tremendous ability to transcend the disadvantages of a scarcity of therapeutic services to overcome this problem in order to promote successful action. MHealth is the use of mobile devices, materials, and associated infrastructure in the area of health maintenance. MHealth offers an optimal platform for real-time and efficient health maintenance and disease prevention that is accomplished by tailored lifestyle improvements (through interactive applications), community-based or clinical treatment roadmaps, and related diagnosis tracking. MHealth system enhances the efficiency, reliability, and suitability of the integrated healthcare and medical outbreak response, primarily through 2 ways: enhanced access to non-clinical healthcare services (including self-testing) and reporting diagnostic results to medical providers and healthcare organizations (Perkel 2017).

Patients report the findings of the self-tests via the mobile device to the hospital and health services and request assessment and medication recommendations based on the actual state of the patient (Fig. 8). These processes include the quick

Fig. 6 Schematic diagram of nanomaterial-based affinity biosensor for coronavirus detection (AuNPs, gold nanoparticles; GR, graphene; NWs, nanowires; AuNIs, gold nickel nanoparticles; FET, field-effect transistor)

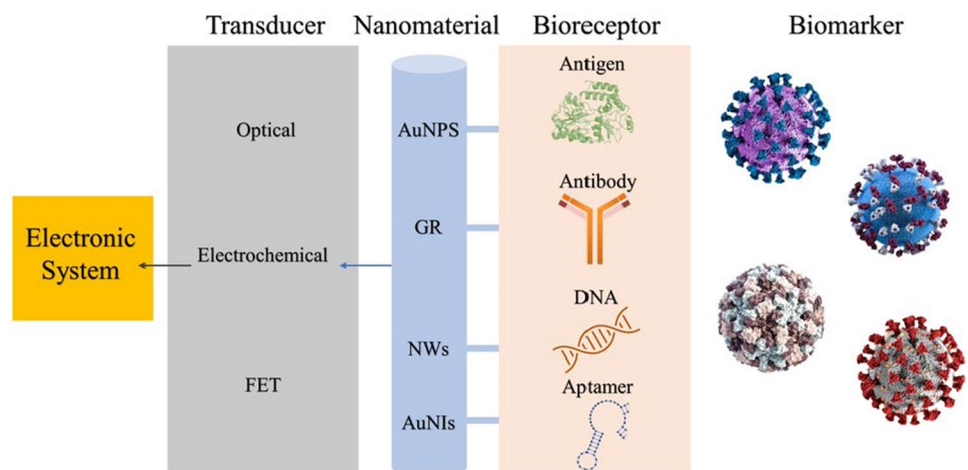
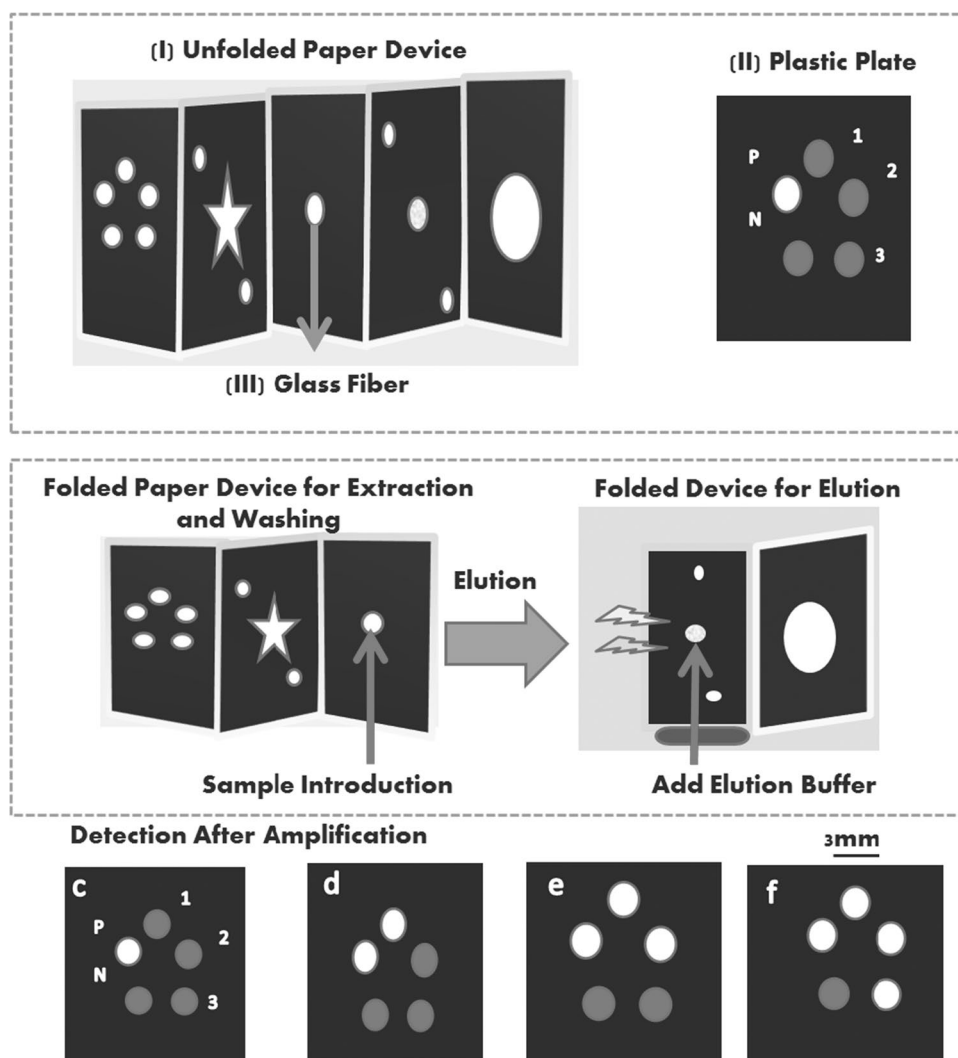


Fig. 7 Paper-based biosensors



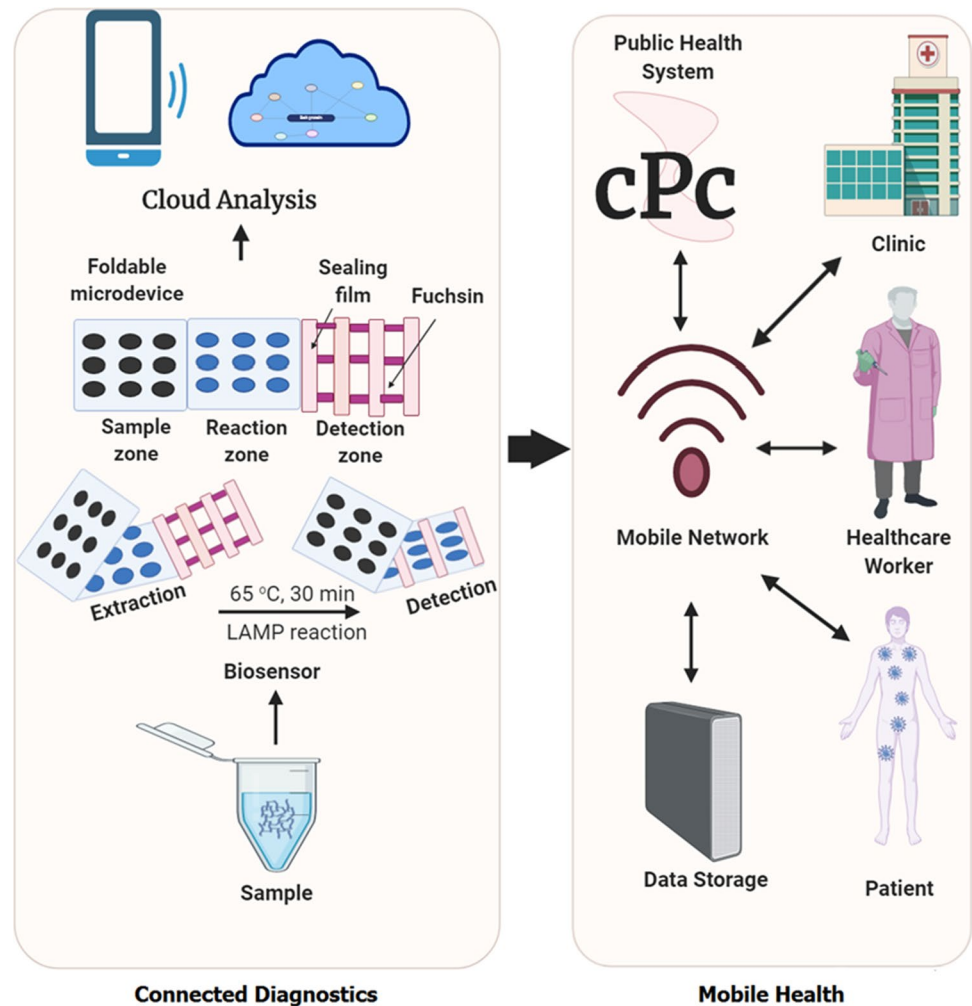
transfer and storing of data and the connection of all relevant parties, all of which entail appropriate resources for technological support and hardware. The exponential advancements of portable networking technologies like 5G and digital computing, such as “big data” principles and “block chain,” increase data transfer and exchange speed and performance. Furthermore, the comprehensive mobile and network application required for them decreases the expense of data processing and transfer. Scientists and medical networks will have the ability to collect and process data with an efficient portable device with sensors/biosensors and wireless links (Perkel 2017).

In addition, the MHealth method will improve productivity by automating inventory and supply chain processes, reduction of workload and paper-related mistakes, and avoiding item loss (Namisango et al. 2016). MHealth has shown its effectiveness in reacting to certain infectious diseases on the media, clinical, and public health. Detailed online prevention, evaluation, and health plan were presented in a report from the UK (Estcourt et al. 2017). Clinical consultations

were conducted online for chlamydia patients who had a link between their history and their pharmacies’ acquisition of antibiotics. The framework combines partner alerts, health promotion, and automated data treatment to prevent the spread of these potentially asymptomatic contagious diseases.

A biosensor can also be a quick (personality testing), rapid (almost real time) diagnostic tool or detection device to determine the appropriate diagnosis targets for contagious diseases (Bissonnette and Bergeron 2017), and to immediately relay the diagnostic effects to the MHealth system, which would dramatically accelerate the patient’s access to treatment and consultation. The identification and implementation of a web-based symptoms and diagnosis reporting application, associated with standardized clinical and epidemiological data gathering, provides a significant potential to increase epidemic monitoring and control (Fallah et al. 2017).

Mobile surveillance can easily identify and handle SARS-CoV-2 and intensify the real-time tracking of outbreak areas (Hayward et al. 2014). In addition, community health agencies

Fig. 8 Biosensor-based MHealth system

will track the disease with the MHealth system in real time and take corrective steps such as geographic separation and strategic material distribution. The mobile system is easy to learn and can be diagnosed by all mobile system users, including prospective patients, medical personnel, and community health agencies. Health professionals can help direct patients' healthcare, and the community health department can better track the crisis and take steps such as prompt patient segregation, health safety, and public service distribution. In accordance with diagnostic biosensors connected to the internet, the mobile networks provide modern approaches for the detection, surveillance, and management of infectious disorders while enhancing health system performance (Fig. 8).

Data analysis and user's privacy protection challenges

Embedded data is used for remote patient treatment and diagnosis (e.g., from smartphones and sensors) (Latif et al. 2017a). This can include details on mobility, vital

physiological signs, blood glucose, body temperature, and various other signals related to the activity. Ye et al. (2020) have built a framework that uses real-time information, including demographic data, accessibility data, disease-related data, and user-generated social media information. This proposed framework, called satellite, will provide a hierarchical community-level risk evaluation that can guide the creation of strategies to tackle the SARS-CoV-2 pandemic.

Google has also used location data from smartphones to display people's movements during the pandemic (Newton 2020). The design of a low-cost framework for detecting SARS-CoV-2 using smartphone sensors is presented in another study (Maghdid et al. 2020). They suggest the use of radiologists' mobile phones for virus detection. They emphasize that the proposed system is more accurate as it uses multi-readings that can capture signs related to the illness from multiple sensing instruments. Another latest study (Ferretti et al. 2020) concluded that SARS-CoV-2's spread is too rapid for manual contact tracing to be contained. Disease monitoring applications (Yoneki and Crowcroft 2014) use contact/location sensor data to address this.

The COVID Symptom-Tracking-Software and the COVID-Near-You-Service are the simplest ones that aim to understand the spread of the disease, particularly mild cases that are not frequently checked in the laboratory. Others, such as Stay-Home-Safe in Hong Kong and the Home-Quarantine-App in Poland (Cyfryzacji 2020), aims to track whether people follow quarantine rules (via geofencing). If they have come into touch with anybody infected, more sophisticated technologies will alert users. For example, there are many common softwares such as China's Close-Contact-Detector-App as has been mentioned by (Kamel Boulos and Geraghty 2020), China's QR health code complementary system (Ye 2020), Singapore's Trace-Together-App. (Lai et al. 2021), and Israel's HaMagen-App. (Cohen 2020). In the above apps, we remember that one important problem is the security of consumer privacy (Calvo et al. 2020; Cho et al. 2020a). Uploading contact data for server-side computing, for example, might build a national social relationship database, particularly in countries where the user can be mandatory. Decentralized Privacy-Preserving Proximity Tracing (DP-3T) (Troncoso et al. 2020) was proposed to address this. This is a smartphone app for users who might have recently come in touch with an infected user that delivers privacy-preserving warnings. Similar features based on homomorphic encryption are provided by TraceSecure (Bell et al. 2020), while Berke et al. provide privacy assurances through the intersection of private sets (Berke et al. 2020). Apple and Google have revealed collaboration focused on Bluetooth to create their privacy-preserving touch tracing standards.

The SARS-CoV-2 pandemic presents specific challenges to communities in developing countries with limited access to healthcare, especially as those people are disproportionately impacted by limited access to public health information (Ahmed et al. 2020; Abouzid et al. 2021). The creation of innovations intended to be internationally inclusive is a key task. This includes an analysis of how certain innovations could affect diverse populations and examine how they could be applied in rural and socially vulnerable regions (Quinn et al. 2014; Latif et al. 2017b; Qadir et al. 2017) and also how they could be misused in such ways. This subsumes a range of functional challenges that naturally differ on the basis of a particular use case. For example, if you are developing a mobile app for touch monitoring, it should be low cost and need limited resources; it should be built with limited network connectivity in mind; it should also accommodate various languages and be open to illiterate users or people with disabilities. We stress that maintaining widespread usability to technical technologies is essential to solving this global pandemic.

Conclusion and future perspective

Since the SARS-CoV-2 virus is already spreading from one person to another around the globe, it is imperative that this infection can be diagnosed early. Biosensing

techniques must be continuously improved in order to meet the rising obstacles in viral diagnosis. It is possible for medical facilities to use the biosensor information to remotely screen the huge populations, such as quarantined individuals, patients confined to long-term care facilities, and those who are at risk in their own homes. The development of biosensors remains challenging, especially with new issues such as data privacy and funding. Therefore, it is essential to proceed with more research on novel biomarkers and mechanisms besides the collaboration with multiple discipline scholars. Future research should focus more on investigating modern properties of materials and study the mechanism and interactions between biomolecules and nanomaterials using nanofilms, electrodes, or new fabricated surfaces.

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Declarations

Ethics approval and consent to participate Not applicable

Consent for publication Not applicable

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