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Biosensors application for SARS-CoV-2 detection

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ABSTRACT

In the light of the rapid diffusion of the coronavirus in the last four years and Vue the hinge of a proper management and prognosis of future possible outbreaks, this systematic review tackled several recent studies on SARS-CoV-2 detection approaches using nanotechnology-based biosensor devices as a successful tool in the early-stage detection of the Coronavirus.

Notably, various biomarkers have shown significant applications of Electrochemical, field effect transistor, surface plasmonic resonance and piezoelectric based biosensors in the SARS-CoV-2 pandemic. These devices are showing instant rapid results (10 seconds), low detection limits (0.22 pM) and high sensitivity for early and effective diagnosis of coronavirus.

The urgent need for early viral detection methods, vital for controlling infection, guiding therapy, and advancing vaccine studies have stressed the importance of biosensors in this field. More research is nevertheless required to streamline the production of these devices, making them more affordable and user-friendly.

Keywords: SARS-CoV-2, EC, FET, SPR, Piezoelectric biosensors

Introduction

Coronavirus is an airborne virus transmitted via aerosols where it remains viable for several hours and causes infection.[1] Many studies using environmental sampling have shown the capability of SARS-CoV-2 to transmit via air, faeces and surfaces.[2] Transmission occurs by direct contact with (1) infected symptomatic patients - without neglecting the potential source of infection by asymptomatic and presymptomatic patients where SARS-CoV-2 shedding starts in the early days of infection before symptoms appear, (2) surfaces contaminated with the virus and (3) contaminated foods.[3-5] Therefore, detection methods improvement to study transmission routes and mechanisms of diffusion is crucial to manage this infectious agent.

Currently, the standard most effective laboratory test used for SARS-CoV-2 RNA virus detection is real-time quantitative polymerase chain reaction (RT-qPCR). Other laboratory tests may include serological testing, viral sequencing and viral culture. Although RT-qPCR is an already established method of diagnosis, nucleic acid amplification is work-intensive and time-consuming. Therefore, a more rapid and effective method is needed for infectious disease diagnosis on a large scale. This gap must be filled to contribute to the proper management of the outbreak by reducing the number of new confirmed SARS-CoV-2 cases and leading to a better prognosis.

Biosensors have proven their useful application in many medical fields and environmental monitoring since the early 1970s.[6] These analytical devices are rapid, non-invasive, efficient and cost-effective. They also provide a continuous assessment, making them good choices when processing a large amount of data. They have been used recently in the study of coronaviruses dissemination.[7] Researchers are continuing to study and develop these biosensors in an effort to boost performance and broaden the variety of applications for them in disease monitoring and diagnosis.

This review article sheds the light on the biosensors as early-stage detection methods in controlling the SARS-CoV-2 pandemic. Despite the accessibility of vaccines, there are still new viruses emerging especially in regions with lower vaccination rates and biosensors can help in promptly containing these outbreaks. In addition, it is still crucial to identify the virus in vaccinated people who have breakthrough infections in order to comprehend the processes of immunity and the viral progression.

Early-stage detection of Coronavirus

Early viral detection methods are required to boost the control of infection, therapy, and vaccine studies during pandemics. Currently, RT-PCR, computed tomography scans of the chest, and lateral flow assays are utilized to diagnose SARS-COV-2 pneumonia. Unfortunately, in severe outbreak zones, several suspected cases may not be confirmed because of hospitals' work overload. Therefore, reliable, rapid response, accessible analytical methods (economically and broadly) and diagnostic techniques are critical to control the current pandemic and prevent further outbreaks in the future.

Several studies have significantly evaluated SARS-CoV-2 detection approaches, including biomarkers and indicators (**Table 3**).[8-10] Single-stranded RNA, membrane proteins (M), envelope proteins (E), spike proteins (S), and nucleocapsid proteins (N) are the most crucial structures to examine in SARS-CoV-2 virus.

These methods are available with high sensitivity for infectious viruses [e.g., nucleic acid-based methods (such as RT-PCR), immunoassays (such as enzyme-linked immunosorbent assay (ELISA), DNA sequencing, and mass spectrometry. However, these techniques require well-trained staff, are high-priced, require sample preparation and purification and are time consuming. The difficulty is also associated in some cases with the inability to cultivate some viruses.

On the other hand, environmental and disease diagnosis and surveillance have improved over the past years by adapting point-of-care testing especially in crowded places and during outbreaks. The need for a rapid, small, effective and reliable device for environmental and clinical monitoring increased the importance of biosensors in this field. They are widely used in viral pathogen detection for early and effective diagnosis, particularly during pandemics.

Table 3: Biomarkers used for SARS-CoV-2 detection.

Biomarker/indicator	Function mode	Other comments
RNA	Most targeted genes: N and S genes	Excellent sensitivity forSARS-CoV-2
Antigen	- Structural proteins whichare; • S (Spike glycoprotein) • M (Membraneprotein) • E (Envelope small membrane protein) • N (nucleoprotein)proteins	
Antibody	Early response: IgM Late response: IgG	Detected after 5 days of symptoms onset (patients at recovering phase)
Monoclonal antibodies (mAbs)	Target SARS-CoV-2 nucleocapsid protein (NP)	The immunoassay microsystem detected effectively SARS-CoV-2 variants

Biosensors

Biosensors are a large concept developed in the early 1970s. These analytical devices use biological elements (such as nucleic acids, enzymes, and antibodies) that are coupled with a transducer and detector. Their applications are necessary in the healthcare system because they are non-invasive, cost-effective and specific. Biosensor applications can be appreciated in many diseases that considerably affect the individual and society (diabetes, heart disease, cancer and infections).[11]

They are also important in sensing different types of organisms (bacteria, viruses and others) that are found in the environment in all types of matter (water, soil and air).

Biosensors are used for the direct detection of SARS-CoV-2 virions or their determining structures. This assay should be particularly sensitive since the concentration of the usual marker is low and a significant portion of the virus particles are enclosed within the host cells. Biosensors have been also used for detecting anti-COVID-19 antibodies to validate the existence of particular antibodies caused by the disease or to measure seroconversion brought on by the illness or immunization. However, highly specific antibodies like IgG and specific antibodies appear in the blood even later and take several days to form, and therefore they are not a useful tool for diagnosing diseases that are still in the acute stages of an illness.

Biosensors are highly selective, fast, can combine more than two biomarkers, provide multiple modes of sensing, are expendable and easy to use, have a long expiration date, are inexpensive and are capable of continuous production. Biosensors utilize different methods and mechanisms for viral detection, including direct detection of the whole virus, detection of RNA or DNA by applying the principles of RT-PCR or PCR (using fluorescent or radioactive probes), and detection of viral antibodies or antigens using microwell-based bioassays.[12] These nanotechnology-based devices prevent the fast dissemination of dangerous pathogens such as coronavirus (SARS-CoV-2) and the transmission of new variants.[7]

Biosensors work by generating a measurable signal of the analyte concentration by integrating a biological recognition element with a physical transducer.[6] The concept comes from the five basic human senses where an input signal is generated by an external stimulus and then data interpretation occurs. Signals can be measured optically (through optic fibres), electrochemically (through electrodes), or through piezoelectric material mechanically (generation of a voltage under mechanical stress), acoustically (through acoustic waves) and electronically (through ion channel receptors). Microbial biosensors commonly use electrochemical approaches that are available in different forms, such as microbial fuel cells, conductometry, amperometry, potentiometry and voltammetry. This type of biosensor senses the analyte through electrodes, leading to catalytic reactions, and then the electrical signal is measured. Other commonly used microbial biosensors transduce their signals optically by photon measurements through optic fibres. This mechanism relies on the measurement of luminescence, colour and fluorescence.[7]

Each biosensor comprises five components: analyte, bioreceptor, transducer, electronics and display. The sample analytes are samples to be detected by biosensors (for example, protein analyte is indicated for biosensors designed to detect protein).

Bioreceptors are part of the biosensor that recognizes analytes. Bioreceptors could be enzymes, aptamers, cells, deoxyribonucleic acid (DNA) and antibodies. After detecting sample analytes by bioreceptors, they generate signals in the form of light or heat, a process called biorecognition. Transducers are elements that convert different forms of energy into measurable signals. This process is known as signalling. Electronics represent the part of the biosensors that prepare transducing signals for display. It comprises a complicated electronic circuit that amplifies and converts an analogue form into a digital form. Next, quantification is processed by the display part of the biosensors. The display part comprises hardware and software that generate results in an understandable view of the user.[13] These results could be presented as graphs, numeric outputs or images depending on the needs of the user (**Figure 1**).

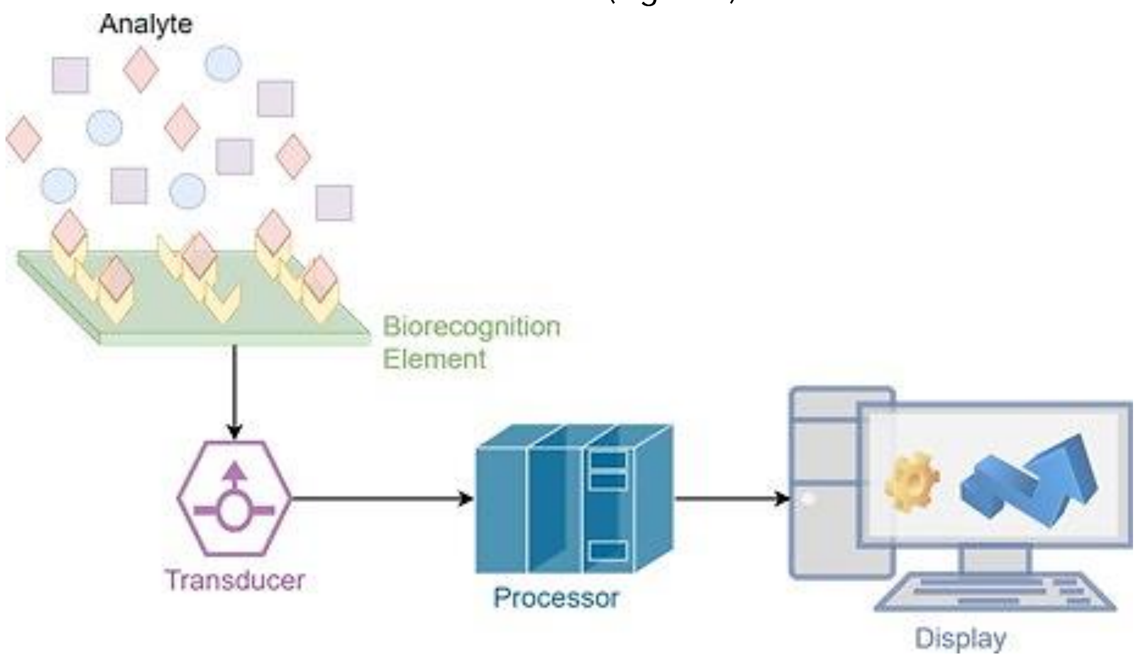

Fig. 1: Components of biosensors

Application of biosensors during coronavirus pandemics:

Biosensors are powerful devices in the early detection of SAR-CoV-2 infection by focusing on the virus antigens to provide knowledge on serious trends of infection and its severity. Importantly, biosensors can provide rapid results and have high sensitivity for the virus antigen; therefore, they may pave the SARS-COV-2 early diagnosis because individuals are being screened in the most crowded areas (airports, hospitals and others). Additionally, a much-desired characteristic of biosensors is providing continuous monitoring of SARS-COV-2 patients in addition to other significant applications (**Table 4**).[7,14-20]

Table 4: Applications of biosensors for the COVID-19 pandemic.

Applications	Significant note
Virus detection	Biosensors have a significant impact on sensing the virus successfully and reliably. Consequently, limiting the virus transmission.
Environmental monitoring and virus concentration measurement in the air	Enzymatic biosensors, Aptasensors and Immunosensors are the most important types of biosensors used to monitor the environment.
Body temperature measurement	Identify the fever which is one of COVID-19 symptoms. In addition, it explores the reason forthe disease.
Wireless medical biosensor patch	It is a new biosensor technology (called biosensor patch 1AX) which is under development, it can be attached on healthcare facility/ patient's chest without any support and can be disposed of easily. In real-time patients, it has the capability to record the body temperature, respiratory rate, ECG trace, and heart rate.
Beneficial in predict future disease	Biosensors may possibly be a part of individual daily life (such as monitoring health at home) and having the ability to predict future diseases.

Over the years, diverse types of biosensors have been used to detect coronaviruses as alternative methods to upgrade the accuracy of SARS-COV-2 detection. Exclusively, during the SARS-COV-2 pandemic, the most commonly used biosensors are EC, surface-enhanced Raman scattering (SERS), FET, and SPR-based biosensors. Additionally, the significance of using these biosensors in SARS-COV-2 diagnosis is accentuated (**Table 5**).[7,15,20-23]

Table 5: Biosensors during COVID-19 pandemic and their Efficiency.

Biosensor's type	Efficiency	Limit of detection
The surface plasmonic resonance (SPR) biosensors (optical sensors)	- Detection of nucleocapsid antibodies (specific against the COVID- 19). - These antibodies assist in detecting patients who have been SARS-CoV-2 immunized. Therefore, contributing also invaccine development. - Dual-functional plasmonic biosensor has encouraged the detection of selective sequence of COVID-19 via nucleic acid hybridization.	- 0.22 pM
FET-based biosensing (Electronic Sensors)	- They have been used in laboratory analysis, on-site diagnostics, and point-of-care tests. - The assessment of the biosensor done onSARS-CoV-2 confirmed cases by utilizing: o Antigen protein o Self-cultured virus o Nasopharyngeal swab samples - Acted efficiently in the diagnosis of COVID-19 in self-cultured medium and samples from nasopharyngeal area.	- 2.42×10^2 copies/mL
EC biosensors	- They have been used in point-of-care test at dwellings and hospitals as they show excellent efficiency in detecting COVID-19 antigen.	- 6 pM
SERS-based Sandwich biosensor	-Usage of different bioprobes in a sandwich structure (NS-ACE2)-(S-Protein)-(ACE2-NS).	- 4.5 fg/mL

Cost-effectiveness, enhanced sensitivity, ease of miniaturization for point-of-care (POC) use and uncomplicated mechanisms are some of the distinctive features of EC biosensors.[24] In 2009, Ishikawa and coworkers developed the first EC biosensor (FET-based immunosensor) to detect SARS. The virus antigen N protein and antibody mimic proteins (AMPs) were used as biomarker affinity binding agents respectively.[25] Another type of EC biosensor (amperometric immunosensor) was used in 2019 to detect MERS-CoV. The main concept of the biosensor is to initiate indirect competition between the free virus in the sample and the immobilized MERS-CoV recombinant spike protein S1 (biomarker). The biosensor was used on 8 carbon electrode surfaces that had been nanostructured with gold nanoparticles to improve the electrode's electrochemical properties and to provide a higher surface area that increased the rate of electron transmission. Successful detection was achieved using the immunosensor of both MERS-CoV and HCoV proteins in spiked nasal samples, which showed many recoveries.[26]

FET biosensors have also proven to be effective and dependable instruments for SARS-CoV-2 detection. Various authors presented biosensing system based on FETs with different advanced nanomaterial for the detection of SARS-CoV-2. Liu and Collaborators concluded that FET SARS-CoV-

2 sensors have relatively low recognition selectivity, but attain great sensitivity.[4,20]

Among optical biosensors, SPR and fluorescence are the most substantiated and assessed transduction techniques.[24] These sensors play a major role during pandemics by using virus high-resolution imaging focused on laser diode excitation.[27] The first SPR-based biosensor was developed in 2009 as a rapid diagnostic method of the severe acute respiratory syndrome. The biosensor used a SARS coronaviral surface antigen (SCVme) that functions as a detection element for anti-SCVme antibody.[28] In the same year, the first SPR fluorescence fibre-optic immunosensor was described for SARS-CoV recognition by detecting the early expressed viral protein (protein N) in human serum.[29,30] Interestingly, the newly developed form of sensors is an optomechanical accessory that can be easily integrated with smartphone cameras (imaging platform resolution: <50 nm).[12] Qu and collaborators developed a fibre optic surface plasmon resonance (FO-SPR)-based label-free approach, which worked well in COVID-19 patient serum with a noticeably shorter time-to-result, taking only 30 minutes as opposed to >1 or 4 hours for the FO-SPR sandwich bioassay and the conventional ELISA, respectively.[31] On the other hand, a manufactured probe using graphene Oxide/Au/fiber Bragg grating (FBG) responded instantly (10-second exposure) to the SARS-CoV-2 S protein in the patients' early-stage saliva (1.6 × 103 copies/mL).[32] A different and potentially useful approach for COVID-19 identification combined the plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) sensing transduction. The dual-functional LSPR biosensor showed a lower detection limit of 0.22 pM, demonstrating a strong sensitivity toward the chosen SARS-CoV-2 sequences.[22] Even though these optical biosensors have shown encouraging results, real sample complexity must be kept to a minimum and the sensitivity can be reduced by impurity detection.

Piezoelectric biosensors rely on the generation of a voltage under mechanical stress.[29] In 2004, horse polyclonal antibodies (against SARS-CoV) were immobilized on the piezoelectric crystal surface and antigen samples were introduced. After adsorption of SARS antigen by the antibody due to ultrasonic oscillation, the changed crystal mass led to a recorded frequency shift. The frequency shift and antigen concentration were proportional in the range of 0.6 to 4 μg/mL. The piezoelectric biosensor showed excellent reproducibility, stability and specificity with a short analysis time of less than 2 min.[33]

Mandal and colleagues constructed a lithium niobate piezoelectric wafer for use as an ultrasonic guided wave sensor. SARS-CoV-2 S protein was immobilized using gold nanoparticles in the piezoelectric biosensor. A signal was produced in response to the total anti-SARS-CoV-2 antibodies. The authors presented their assay as a platform rather than providing analytical details like the method's sensitivity or limit of detection.[34] Another research study presented a wearable face mask with a piezoelectric MEMS-based (Mirco Electro Mechanical Systems) biosensor integrated for the purpose of early SARS-CoV 2 virus droplet detection. The authors claimed many advantages of their invented method including a rapid detection time (0-8min), a low cost (10$) and a limit of detection of 79 ng/ml.[35] According to Pahonka (2022), the major benefit of the piezoelectric platform is the ability to create a label-free assay specifically measuring the mass of the analyte caught on the biosensor surface by determining the oscillation frequency dropping due to the bound mass. This review study concluded that piezoelectric biosensors are still rarely used in point-of-care tests for the diagnosis.

Multi sensors (prototyping biosensors) also play a substantial role in prescribing medicine for SARS-COV-2 because they provide knowledge about the levels of numerous pro- and anti-inflammatory processes, which is crucial to construct personalized treatments. For example, plasmonic nanosensors can detect 6 cytokines [interleukin (IL)-2, IL-6, IL-4, IL-10, TNF-α, and IFN-γ]. The information given by these devices must be combined with patient data (such as age, comorbidities, microbiology findings and treatments) to evaluate the patient risk of having a poor prognosis. Furthermore, biosensors may be crucial to identify problems such as coinfections that are frequently observed in immunosuppressed individuals. These sensors provide more information concerning real-time cytokine-antibody binding than traditional ELISA. Interestingly, the time required to operate is only 40 min, which will facilitate clinical decision-making in emergency circumstances. Therefore, multiple sensors could boost the benefits of anti-inflammatory therapies while diminishing adverse consequences.[33,36,37]

Biosensors are analytical instruments with great promise that can be used for field, point-of-care, and a variety of outdoor applications. It is in-vitro, portable, and offers real-time analysis during sample screening on-site. These features make it a good substitute for traditional diagnostic equipment. Patients can easily quarantine or self-isolate, which would considerably reduce the danger of infection and lessen the strain on medical staff. It would also greatly prevent further transmission. Even in the event that the COVID-19 pandemic is successfully contained, research results pertaining to the identification of other infectious diseases can be readily used and have real-world applications.

Conclusion

Although culture and molecular methods were frequently used in clinical and environmental research studies during the SARS-CoV-2 pandemic, development of diagnostic and detection methods that address the "ASSURED" (affordable, specific, sensitive, user-friendly, rapid, robust, equipment-free deliverable to end-user)" criteria is needed.

Effective viral sensors that are portable, small, and simple to use are desperately needed. They must also have excellent selectivity, cross-sensitivity, and quick reaction times. Additional downsizing may be essential to creating a portable COVID-19 diagnostic tool, and it should be easy enough to use in the field and on-site without requiring operators to have specialized training.

While more work needs to be done to solve the industrial feasibility and create the technological instruments that regulate the biosensors, the primary research on biosensors for COVID-19 diagnosis produced some encouraging ideas. Additional biosensor research would simplify the production of devices with lower prices and less user needs. Thus, the development of affordable, high-performing point-of-care (PoC) devices that can provide dependable, prompt, and robust responses is crucial and essential.

Competing interests:

The authors declare that they have no competing interests.

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List of abbreviations:

SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus-2
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
COVID-19	Coronavirus disease-2019
RNA	Ribonucleic acid
RT-qPCR	Real-Time Quantitative polymerase chain reaction
PCR	Polymerase chain reaction
RT-PCR	Real-Time polymerase chain reaction
N protein	Nucleocapsid protein
DNA	Deoxyribonucleic Acid
HCoV	Human Coronavirus
ELISA	Enzyme-linked immunosorbent assay
EC	Electrochemical
FET	Field effect transistor
SPR	Surface plasmonic resonance
SERS	Surface Enhanced Raman Scattering
POC	Point of Care
AMPs	antibody mimic proteins
SCVme	coronaviral surface antigen
MEMS	Mirco Electro Mechanical Systems
IL	Interleukin
TNF- α	Tumor necrosis factor alpha
INF- γ	Interferon gamma

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