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Review

Next-generation nanophotonic-enabled biosensors for intelligent diagnosis of SARS-CoV-2 variants

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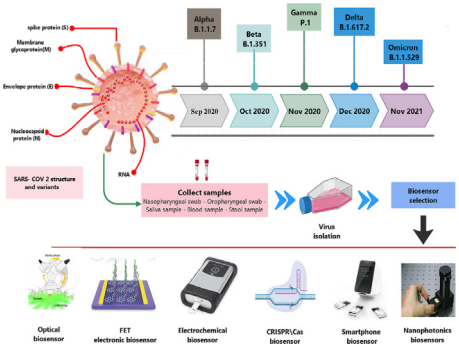
HIGHLIGHTS

- Variations in SARS-CoV-2 with time and environmental factors are detailed
- Evolution and state-of-the-art SARS-CoV-2 variants detection is elaborated
- Merits of nanophotonic-enabled point-of-care biosenor for monitoring of COVID-19 are highlighted
- Integration of AI with nanophotonic biosensors for prompt/precise/smart SARS-CoV-2 detection is explained

GRAPHICAL ABSTRACT



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ABSTRACT

Constantly mutating SARS-CoV-2 is a global concern resulting in COVID-19 infectious waves from time to time in different regions, challenging present-day diagnostics and therapeutics. Early-stage point-of-care diagnostic (POC) biosensors are a crucial vector for the timely management of morbidity and mortalities caused due to COVID-19. The state-of-the-art SARS-CoV-2 biosensors depend upon developing a single platform for its diverse variants/biomarkers, enabling precise detection and monitoring. Nanophotonic-enabled biosensors have emerged as 'one platform' to diagnose COVID-19, addressing the concern of constant viral mutation. This review assesses the evolution of current and future variants of the SARS-CoV-2 and critically summarizes the current state of biosensor approaches for detecting SARS-CoV-2 variants/biomarkers employing nanophotonic-enabled diagnostics. It discusses the integration of modern-age technologies, including artificial intelligence, machine learning and 5G communication with nanophotonic biosensors for intelligent COVID-19 monitoring and management. It also highlights the challenges and potential opportunities for developing intelligent biosensors for diagnosing future SARS-CoV-2 variants. This review will guide future research and development on nano-enabled intelligent photonic-biosensor strategies for early-stage diagnosing of highly infectious diseases to prevent repeated outbreaks and save associated human mortalities.

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Contents

1. Introduction

In early 2023, there had been >758,390,564 confirmed cases of the new coronavirus disease (COVID-19) caused by SARS-CoV-2, including 6,859,093 deaths, according to the World Health Organization (WHO). Considering the rapid spread of the virus, a total of 13,226,873,459 vaccine doses were administered. Additionally, variants of SARS-CoV-2 that have greater transmissibility, pathogenicity, and potential for immune evasion challenge existing diagnostic methods (Harapan et al., 2020; Kasibhatla et al., 2020). Strict rules were implemented to control the spread of the disease. Frequent hand washing and maintaining social distance by avoiding close contact with others, especially in crowded places, were encouraged. Many businesses and educational institutions were forced to close or drastically reduce in-person interactions and shift to a remote workforce. The inclusion of SARS-CoV-2 would have prevented these catastrophic outcomes. The main challenge encountered in stopping the spread of COVID-19 was the inaccessibility of fast virus tests (Huang et al., 2020; Ruiz-Hitzky et al., 2020; Baloch et al., 2020).

The development of dependable and swift diagnosis procedures is vital, as scale-based diagnostic abilities are crucial in controlling infections and reducing mortality rates (Chaudhary et al., 2022a). If no immunizations or treatments can efficiently contain the spread of the disease, the most effective way to manage it is by isolating all infected individuals, whether they display symptoms or not (Rai et al., 2021; Ahmed et al., 2022; Taha, 2021; Taha et al., 2021). Biosensors are highly beneficial in many essential areas, such as medicine, food safety, environmental monitoring, security, pharmaceuticals, and forensics (Chaudhary et al., 2022c, 2023a, 2023b; Sonu, 2022). It is estimated that around 70 % of healthcare decisions are supported by diagnostic technology, making this market a major biosensor market (Ngo et al., 2017).

The revelation of the molecular profile of a patient could play a crucial role in the advancement of precision medicine. Wearable biosensors that are affordable and easy to use are likely to be useful as health tracking devices for individuals. The integration of automated and autonomous biosensors into public infrastructures, such as transportation nodes, educational institutions, workplaces, etc., is planned to increase public safety by warning the public about biological risks. Connected via the "internet of things," these devices have the potential to provide massive spatio-temporal information at the level of a whole population (Shrivastava et al., 2020; Ho et al., 2020). In addition, the use of nanobiotechnology for the detection of the SARS-COV-2 virus has been explored, including components of biosensing, nanomedicine, and nanovaccine (Bidram et al., 2021). In the same manner, there has been an increase in expectations placed on microbiology laboratories located within hospitals to produce accurate and reliable test results for their patients. Several factors have contributed to this stress, including demands from physicians for same-day test results, an increase in the number of samples, and the increasing organism resistance, etc. (Keighley et al., 2021). Rapid diagnostics on site make patient identity and contact tracking more efficient. However, such diagnostic tools do not yet exist. Although immunogenic lateral flow tests are quick, portable, and inexpensive, they are not ideal for detecting early-stage viruses (Sheridan, 2020). Developing a test method with good selectivity requires understanding the structure and function of the virus. The "virions" comprise the entire viral particle, including the genetic material (nucleic acids) and its protective outer coating. DNA and RNA are the genetic materials of most viruses, and nucleic acids can be single- or double-stranded (van Belkum et al., 2019; Taha et al., 2019). In this review, the existing literature on emerging modern variants of SARS-CoV-2 is reviewed, discussing the state-of-the-art and recent advances in biosensor techniques for accurately detecting SARS-CoV-2 biomarkers and offering a critical analysis of both, along with the difficulties and prospects of creating biosensors for diagnosing COVID-19 and other viruses. The taxonomy of current research on SARS-COV-2 variants evaluation, structures, and biosensor diagnosis is depicted in Fig. 1.

2. SARS-CoV-2: a highly infectious and evolving virus

This section describes the SARS-CoV-2 virus evolutions and the appearance of new variations. It highlights the necessity of early discovery and monitoring novel variations to restrict viral propagation. SARS-CoV-2 is a highly infectious respiratory virus that was first identified in December 2019 in Wuhan, China, and has since spread worldwide, leading to a global pandemic. It is mainly transmitted by infected people's respiratory drops and aerosols and can cause severe respiratory diseases and potentially fatal complications in some people (Azuma et al., 2020). The virus evolves over time and new variants have emerged that may be more transmitted, virulent or resistant to existing vaccines and treatments. These concern variants include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529), which are associated with increased transmission and severity (Aleem et al., 2021).

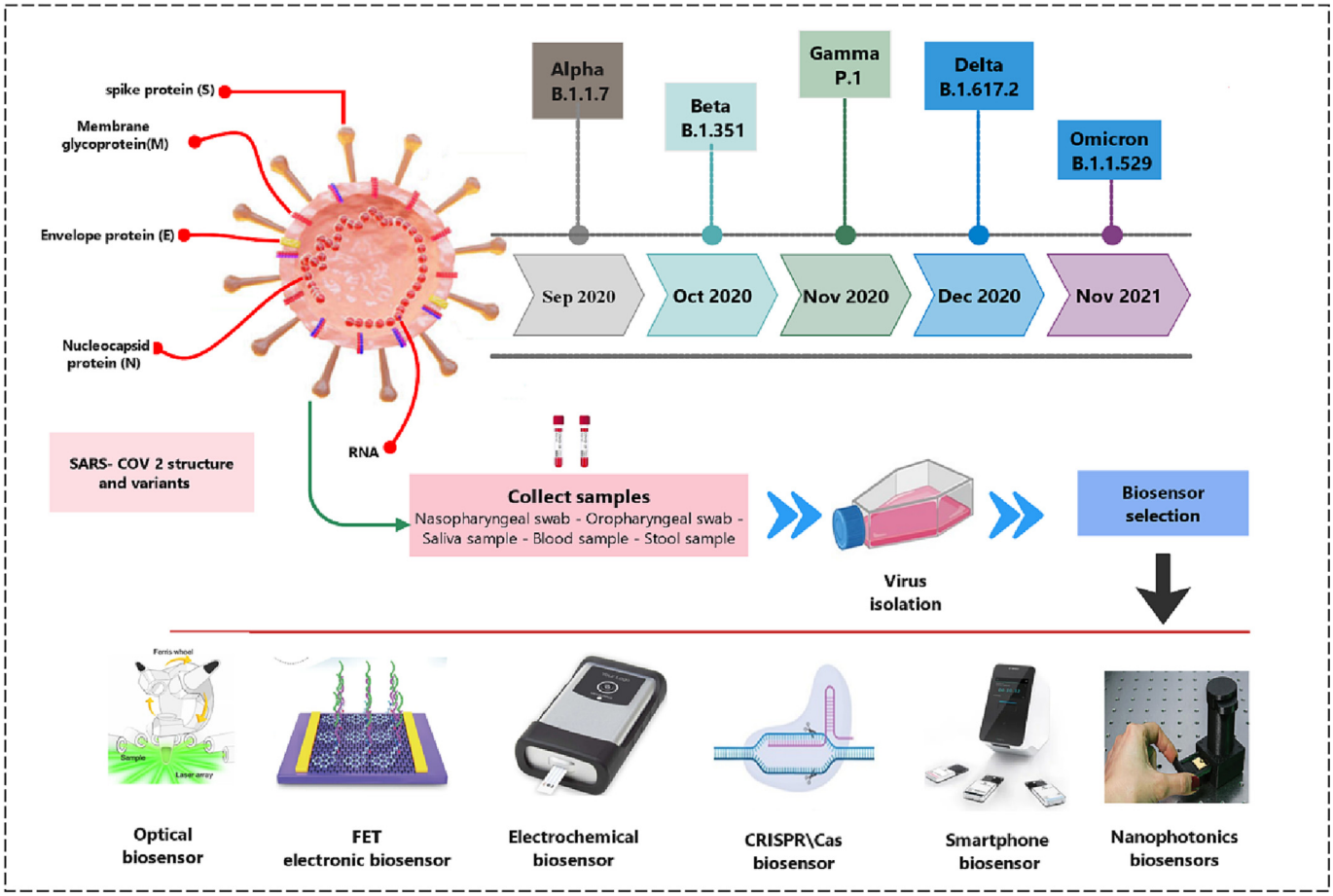

Fig. 1. Taxonomy of studies for evaluation, structures, and biosensors diagnosis of SARS-COV-2 variants.

2.1. Current state of SARS-CoV-2 and its variants

In September 2020, several new variants of SARS-CoV-2 suddenly appeared in locations without a previous connection. The B.1.1.7 mutation was initially identified in Britain (Tang et al., 2021). Another mutation that emerged in South Africa was Beta (B.1.351), Delta variant (B.1.617) in India, and Coronavirus Gamma variant (P.1) in Brazil (Samarasekera, 2021; Thye et al., 2021). Recent studies have revealed several variants of SARS-CoV-2, including variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and recently discovered Omicron (B.1.1.529) variants. The Omicron mutation is the most mutated strain of SARS-CoV-2, with 50 mutations in its genome, including 30 in the spherical protein (S). This increase in mutations has increased transmission and resistance to partial immunity caused by current COVID-19 vaccines and antibody-based treatments (Tang et al., 2021; Samarasekera, 2021; Thye et al., 2021). The spike protein, which allows viruses to enter host cells and is the target of modern vaccines, differs for each virus type. Delta and omicron SARS-CoV-2 strains have mutations in the spike protein, making them more contagious. These changes may affect the spikes protein receptor-binding domain (RBD) and its interaction with angiotensin-converting enzyme 2 (ACE2), which could alter cell entry, viral immune evasion, and immunogenicity (Watanabe et al., 2020). Omicron is notable because it has three different sub-lineages (BA.1, BA.2, and BA.3) found almost simultaneously, even though they are similar to Alpha, Beta, Gamma, and Delta. Scientists have recently looked at the ability of the Omicron BA.4 and BA.5 sub-lineages of Omicron BA.1-infected people. It found that the potential of vaccinated people to neutralize BA.4 and BA.5 had a three-fold reduction (Haseltine, 2022; Tallei et al., 2022), and unprotected people had a seven-fold decrease. Thus, future Omicron sub-lineages are unlikely to be protected against previous infections, and these variations BA.4 and BA.5 might cause new ones (Lewnard et al., 2022; Khan et al., 2022). Overall, Omicron is thought to have significantly more mutations in its receptor binding area (RBD) and family chylomicronemia syndrome (FCS), resulting in higher infection compared to the original SARS-CoV-2 strain and subsequent variants such as Delta (Zahradník et al., 2021). Fig. 2 illustrates a comparison of various SARS-CoV-2 variants in terms of infection rates, symptomatic cases, hospitalizations, and cumulative deaths.

2.2. Variants of concern (VOC) and spike mutations

A mutation refers to a single alteration in the genetic code or genome of a virus. While mutations are common, they typically do not significantly impact the properties of the virus. However, several mutations in SARS-CoV-2 have been found to affect the virus's properties and response to the pandemic. Initial analyses have suggested that at least one mutation shared by three concerning variants could potentially enhance the virus transmissions efficiency (Ünlü et al., 2021). The first variant had the D614G mutation, which made it more infectious, while the second variant had the N501Y mutation, which appears to make it more transmissible (see Fig. 3). Both variants have been detected in many countries worldwide, causing concern among public health officials. In the BA.1 lineage, the Omicron variant has >60 mutations. Of these, 38 are in the spike protein (S), two are in the membrane protein (M), one is in the envelope protein (E), and six are in the nucleocapsid protein (N). Also, the BA.2 lineage has 57 mutations, 31 of which are in the S protein. BA.2 has a different N-terminus than BA.1. The S protein is essential when attaching to host receptors like ACE2 (Garcia-Beltran et al., 2021; Wang et al., 2022; Araf et al., 2022). The B.1.1.298 lineage, like the second N439K lineage, B.1.258, is

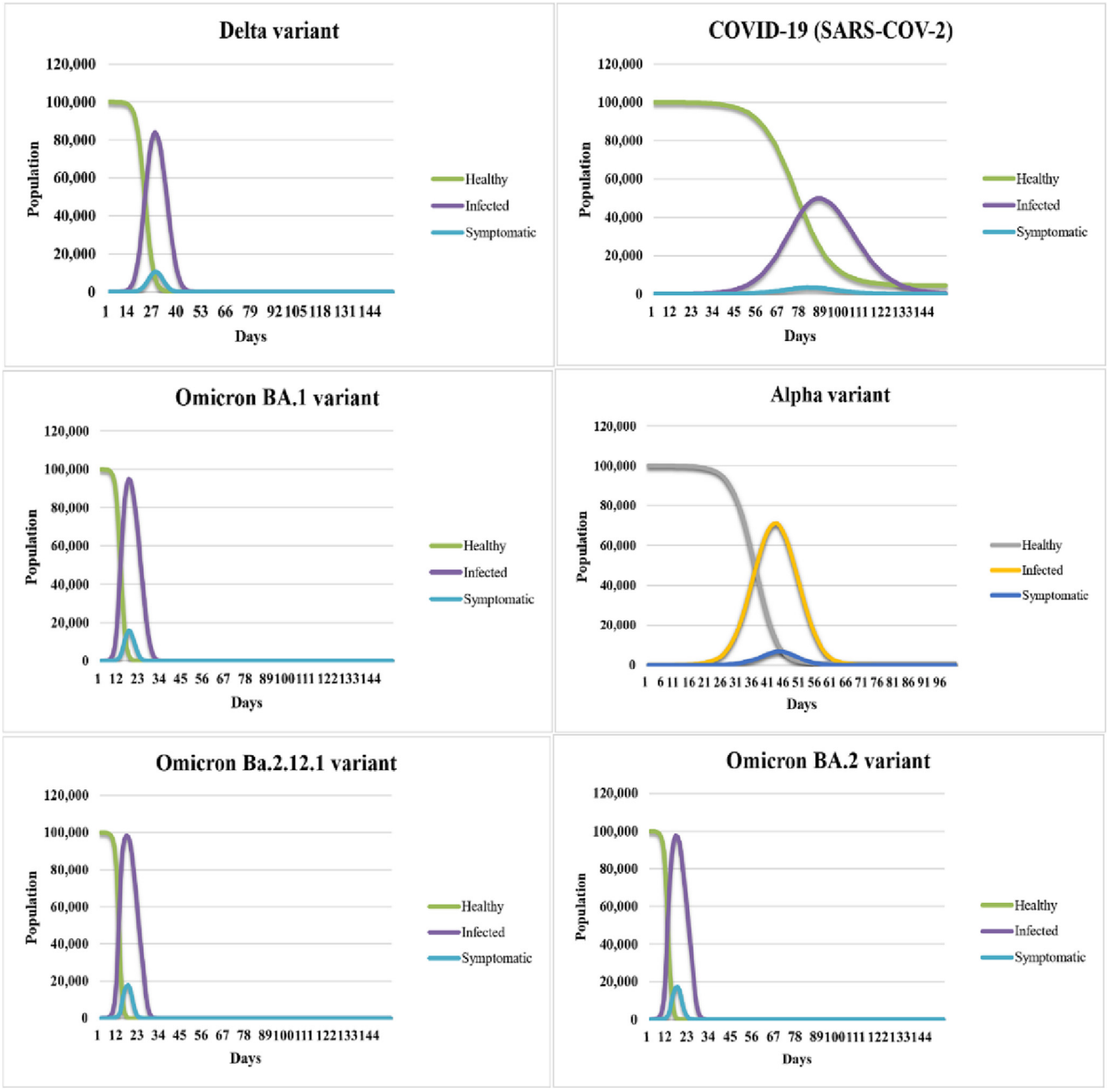

Fig. 2. Compares the population (healthy, infected, symptomatic) across the six variants of SARS-CoV-2 strains per day, with data obtained from https://ourworldindata.org.

characterized by deletions in the amino-terminal domain (NTD) [69, 70]. This deletion has occurred multiple times in the global SARS-CoV-2 population. Deletions in 69–70 are associated with increased infectivity and are believed to impact the configuration of a prominent NTD loop (Meng et al., 2021). Understanding the dynamics of mutation and infection requires examining virus sizes, shapes, and structures. Most investigations on SARS-CoV-2 in the literature have focused on mutations in the spike protein, which is critical in binding to receptors and fusing with cell membranes to infect a human host. The spike protein is separated into two parts, N-terminal S1 and C-terminal S2, which have distinct but complementary activities and are present in the viral envelope (Abraham, 2020; Li, 2015; Gui et al., 2017). Several tests have shown that mutations in the spike glycoproteins of SARS-CoV-2 variants improve the fitness of the spike protein. The structure of the Gamma variant's N-terminal domain has changed a lot, which may explain why convalescent sera don't work as well to neutralize it. These spike mutations tell us a lot about how weak spike proteins are built, how they work, and how they react with antibodies (Resende, 2021; Resende et al., 2021; Zhu et al., 2019; Mannar et al., 2022).

Ultimately, it emphasizes the need for monitoring and understanding SARS-CoV-2 development, mainly introducing new variations and spike mutations, to successfully manage the virus's propagation and create viable therapies. The mutation from aspartate (D) to glycine (G) at 614 is particularly significant because it is located in the receptor binding domain (RBD) of the spike protein and plays an important role in the virus' ability to enter human cells. Changes in amino acid composition resulting from these mutations can increase the infectivity and transmission of viruses by stabilizing the open structure of spike proteins as shown in Fig. 3.

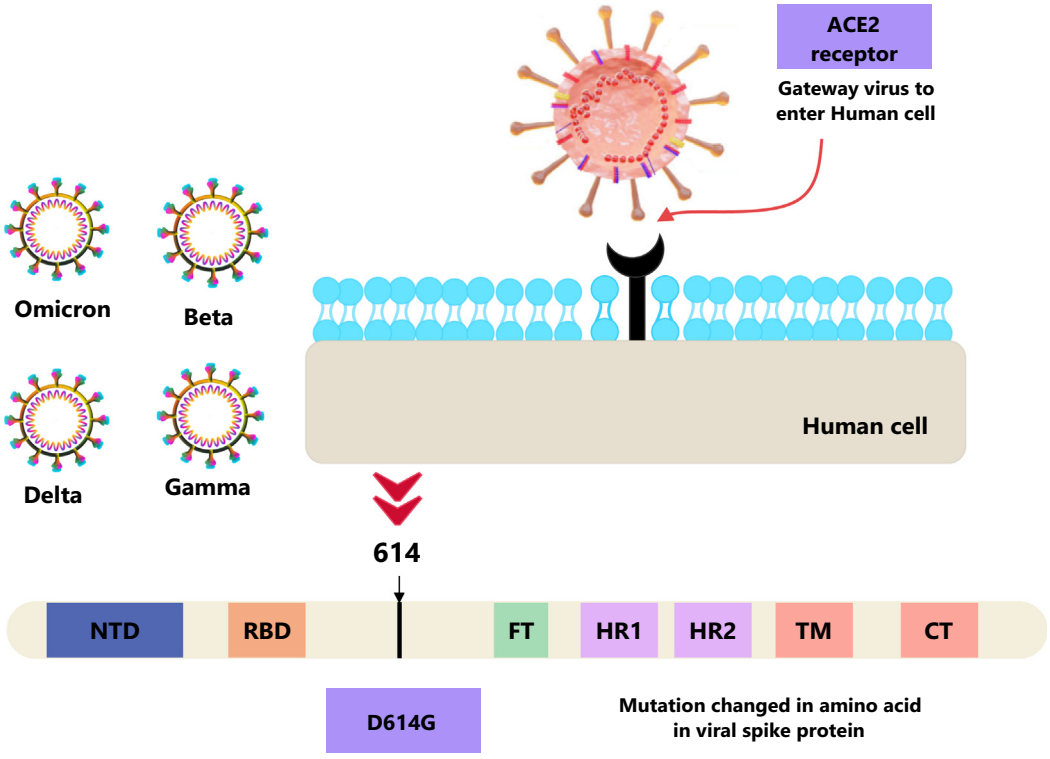

Fig. 3. Illustrates the impact of the D614G mutation on the amino acid composition of the viral spike protein at position 614, which has been changed from aspartate (D) to glycine (G).

3. Biosensors for SARS-CoV-2 detection

3.1. Optical biosensors and their potential for SARS-CoV-2 detection

Optical affinity biosensors use biomolecular receptors that can interact specifically with an analyte and an optical readout mechanism to turn this interaction into a measurable output. Spectroscopic biosensors, like Raman, infrared, and chiral, get their output directly from the optical properties of the analyte (Novotny and Hulst, 2011; Li et al., 2019; Ruiz-Vega et al., 2021). Photonic biosensors make use of evanescent fields to isolate optoelectronic components from liquid samples, making them useful for analyzing analytes. The evanescent field has an exponential decline, with a decay length on the order of hundreds of nanometers perpendicular to the sensor surface. Surface confinement is a crucial component that enhances light-matter interaction and provides precise spatial control of measurements (Altug et al., 2022; Liedberg et al., 1995; Homola and Piliarik, 2006). Two strategies, direct detection of SARS-CoV-2 viruses for early diagnosis and population screening and identification of PCR-free viral RNA, are used by biosensors based on bimodal waveguide (BiMW) interferometric technology. A photonic nanosensor that targets the SARS-CoV-2 RBD region using bioengineered nanobodies (Nb) has been developed and bimodal waveguide (BiMW) interferometric technology is used for rapid and direct measurement of the RBD of the SARS-CoV-2 virus (Ruiz-Vega et al., 2022). A microfluidic device that can directly see the levels of SARS-CoV-2 antibodies in a way that doesn't require any instruments (Cherusseri et al., 2022). Magnetic and polystyrene microparticles are used to bind to SARS-CoV-2 antibodies simultaneously, which reduces the incidence of free particles escaping from magnetic separation and shortens the accumulation length at a particle dam. The results show a LOD of 13.3 ng/ml at 70 min and a rapid mode of 57.8 ng/ml at 20 min (Wu et al., 2022). In Payne et al., it was demonstrated that the unique vibration characteristics of the surface modified by the S-protein binding peptide can be identified and quantified by the SARS-CoV-2 SERS sensor, which is based on ACE2 as a viral protein capture probe. The LOD was reported to be 300 nM (Payne et al., 2021). Sensitivity detection of the SARS-CoV-2 nucleocapsid protein (N protein) is achieved using surface plasmon resonance (SPR) methods that are boosted by nanoparticles. The method uses AuNPs with diameters of 100 nm and this enhancement of SPR provided by these large nanoparticles results in the lowest limit of detection (LOD) of the SARS-CoV-2 N protein (85 fM) ever obtained by SPR as per Yano et al. (2022). Researchers proposed using hyperspectral imaging based on optical imaging spectroscopy to detect SARS-CoV-2 spike samples of 5 μl of fluid at the pixel, droplet, and patient levels using spectral characteristic descriptors and partial least squares discriminant analysis in the visible and near infrared, achieving 100 % sensitivity as per Gomez-Gonzalez et al. (2022). COVID-19 Low-cost optical diagnostic for rapid testing is a colorimetric biosensor manufactured on cotton swabs and modified with an enzyme of angiotensin-converting enzyme 2 (ACE2) that detects SARS-CoV-2 in 5 min. It is manufactured from micro-sized gold nanoparticles and changed with human ACE2. The COLOR method saw very low viral particle loads at LOD 0.154 pg ml^{-1} (Ferreira et al., 2021). Here, a single pot RT-LAMP based on a multifluid probe assay was reported to detect fragments of the SARS-CoV-2 ORF1ab and N gene. The results were a sensitivity of 20 copies/l for ORF1ab gene fragments and a sensitivity of 2 copies/l for N gene fragments using two primer sets and two molecular beacon probes (MB), each labeled with a different fluorophore (Talap et al., 2022). A study shows an integrated silicon photonic crystal microarray structure for multiplexed sensing and the multimode interference coupler architecture for COVID-19 testing (Asghari et al., 2021). Fig. 4 shows four different state-of-the-art optical sensors for detecting SARS-CoV-2 variants.

3.2. Field effect transistors (FET) electronic biosensors

A field-effect transistor (FET) electron sensor is only one of many potentiometric techniques. Separately from the biological recognition element, an insulator layer (like SiO2) functions as a selective transducer for the target molecule. Electrostatic surface potential variations in semiconductors are used to identify nucleic acids and proteins by correlating them with changes in the charge distribution on the surface (Kaisti, 2017). The study discusses the use of a field effect transistor (FET) biosensing

unit to detect the SARS-CoV-2 virus in clinical samples using a transistor biosensing unit. As sensor, a graphene sheet field effect transistor (FET) immobilized with an antibody specific for the SARS-CoV-2 spike protein was used. Sensor output was determined using an antigen protein cultured virus and a nasopharyngeal swab from a patient with COVID-19. Detection in medical tests was possible at a concentration of 2.42 10^2 copies/ml 62. Researchers show analysis of nucleic acids directly on graphene field effect transistors (g-FETs) using dual Y-shaped DNA probes.

The SARS-CoV-2 nucleic acid is targeted by adapted Y-dual probes on g-FET, allowing for a high recognition ratio and a detection limit (0.03 copies l^{-1}) 1–2 orders of magnitude lower than current nucleic acid assays. The assay is the first to perform a direct 5-in-1 pooled nucleic acid test in <1 min (Kong et al., 2021). Develop a biosensor based on viral receptors for rapid screening of COVID-19 that is sensitive and portable. A dual-gate field effect transistor was used to boost the performance of a viral receptor-based biosensor, which is notoriously insensitive. The optimized biosensor was created using a synthetic virus that resembled SARS-CoV-2 in size, structure, and composition. The new biosensor recognized SARS-CoV-2 with a sensitivity of 165 copies/ml, which is on par with molecular diagnostic assays, and did so in just 20 min (Park et al., 2022). These sensors are also inexpensive and user-friendly.

However, coronavirus samples require extensive pretreatment and filtering prior to a final diagnosis. A digital platform can achieve a binary classification based on artificial intelligence at the level of identifying a single marker/virus in 0.1 ml. Validated by a total of 240 tests, including a small-scale clinical study, diagnostic sensitivity, specificity, and precision are 99.2 %. Saliva, blood serum, and swabs can be tested with the flexible immunometric system, identifying the SARS-CoV-2 virus, spike S1 and antigen proteins.

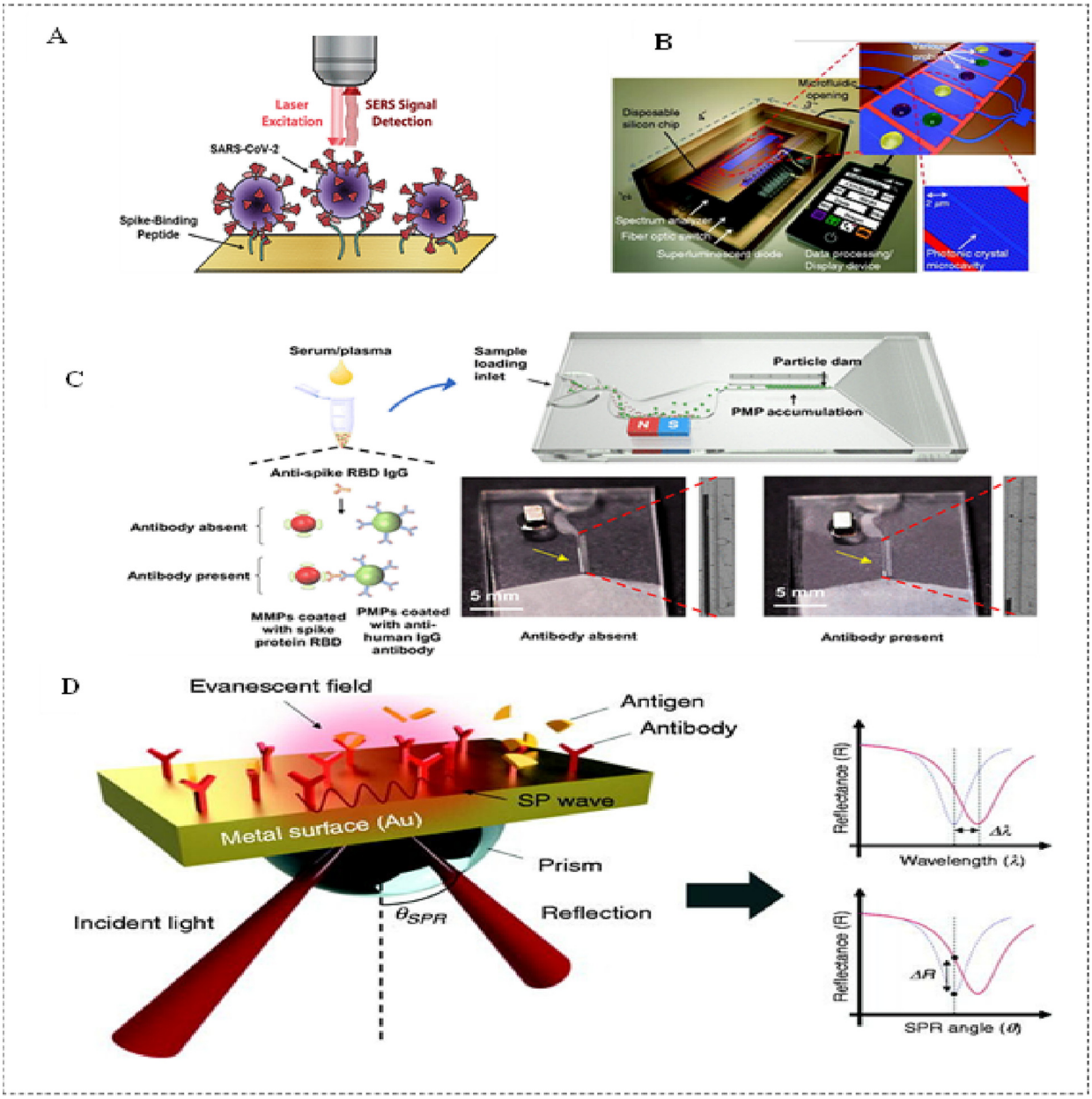

Fig. 4. Showcases the latest advancements in optical sensors for detecting SARS-CoV-2 variants. These include: A. a SERS biosensor, reprinted with permission of Payne et al. (2021) Copyright 2021, ACS sensors. B. a silicon photonic crystal microarray structure for multiplexed sensing, reprinted with permission of Asghari et al. (2021) Copyright 2021, Applied Physics Reviews. C. a microfluidic particle dam for directly visualizing SARS-CoV-2 antibody levels in COVID-19 vaccinees, reprinted with permission of Wu et al. (2022) Copyright 2022, Science Advances, and D. a standard SPR-based biosensor configuration. Reprinted with permission of Asghari et al. (2021) Copyright 2021, Applied Physics Reviews.

BioScreen is compact, since it consists of a disposable cartridge and a portable electronic reader that can be synced with a smart device. Suitable molecular handling and a quick test time of 21 min are two of the many benefits of this method (Macchia et al., 2022). Fig. 5 describes the steps taken to develop a portable electrical biosensor that uses virus receptors, such as SARS-CoV-2 replication and infection, the synthesis of the synthetic virus using microfluidics and the portable electrical biosensor.

3.3. Electrochemical biosensors

Electrochemical biosensors are evidence biochemicals that convert a voltage or current into an analytically valuable signal (Chaudhary et al., 2022c; Cherusseri et al., 2022). An electrochemical biosensor device (eCovSens) was designed to detect COVID-19 spike protein antigens in spit samples to detect the sensitive COVID-19 antibody. A gold nanoparticle was deposited on a fluorine-doped tin oxide surface and measured electrical conductivity. The results show the sensitivity levels of the assay of (90 and 120) fM (Mahari et al., 2020). Electrochemical biosensors have been reported to detect MERS-CoV. This experiment aims to demonstrate the successful use of a variety of gold nanoparticles that have been modified for use with carbon electrodes. It used an antibody specific for MERS-CoV during the screening process to recognize the virus spike protein (S1). The virus was detected 20 min after being isolated and purified (Layqah and Eissa, 2019). Developed a low-cost biosensor composed of pencil graphite electrodes that was able to detect the presence of SARS-CoV-2 on a minute scale (de Lima et al., 2021). Similarly, a study shows that an electrochemical impedance spectroscopy biosensor can be used at the point of care to detect SARS-CoV-2 and variant B.1.1.7 in real time (Torres et al., 2021). Another study reported developing an electrochemical sensor chip based on a paper that was <5 min, inexpensive, easy to apply and quantitative detection of SARS-CoV-2. Methods have been used using AuNP coated with ssDNA encoding a phosphoprotein found in viral nucleocapsids (N-gene) (Alafeef et al., 2020). Fig. 6 shows the electrochemical sensor instrument for the SARS-COV-2 virus and describes its underlying working principle. The electrochemical sensor has a significant amount of potential to convert a biochemical signal to an electrical one because of the many benefits it offers in the evaluation of a biological sample. On the other hand, isolating and purifying the selection might be a time-consuming process.

3.4. CRISPR sensors

Genome editing and nucleic acids can be detected with the use of CRISPR technology combined with the many Cas enzymes associated with CRISPR. It is necessary to isolate the nucleic acid SARS-CoV-2 to confirm the presence of COVID-19 (Rahman et al., 2021). A study shows that CRISPR-Cas13d provides a broad-spectrum antiviral (BSA) that inhibits >99 % of viral titers from various human coronaviruses and variants of SARS-CoV-2 (Zeng et al., 2022). Recent advances in CRISPR-Cas13 transcription amplification methods have facilitated the investigation that allows the detection of SARS-CoV-2 and its mutant versions. The target-activated ribonuclease activity of CRISPR-Cas13a helps to produce sensitive amplification signals, and this is made possible by the aptamer of light-up RNA. In addition to influenza viruses such as H1N1, H7N9, and H9N2, the RNA viral test can detect Coronavirus, SARS-CoV-2, Middle East respiratory sickness (MERS) and SARS viruses. Furthermore, the

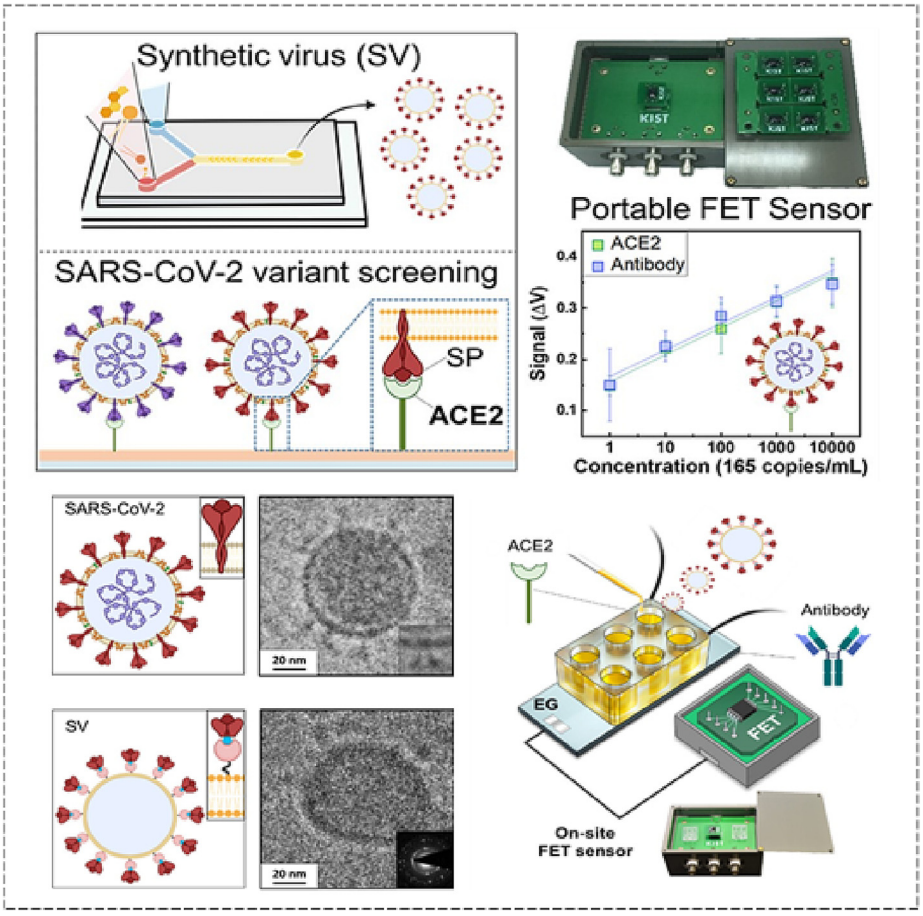

Fig. 5. Represented A portable electrical biosensor is built using virus receptors, such as replication and infection of SARS-CoV-2, and synthesis of the synthetic virus using microfluidics and the portable electrical biosensor. A synthetic SARS-COV-2 with the SP1 spike protein bound to the avidin molecule is available for cryo-electron microscopy. Reprinted with permission of Park et al. (2022), Copyright 2022, Nano Letters.

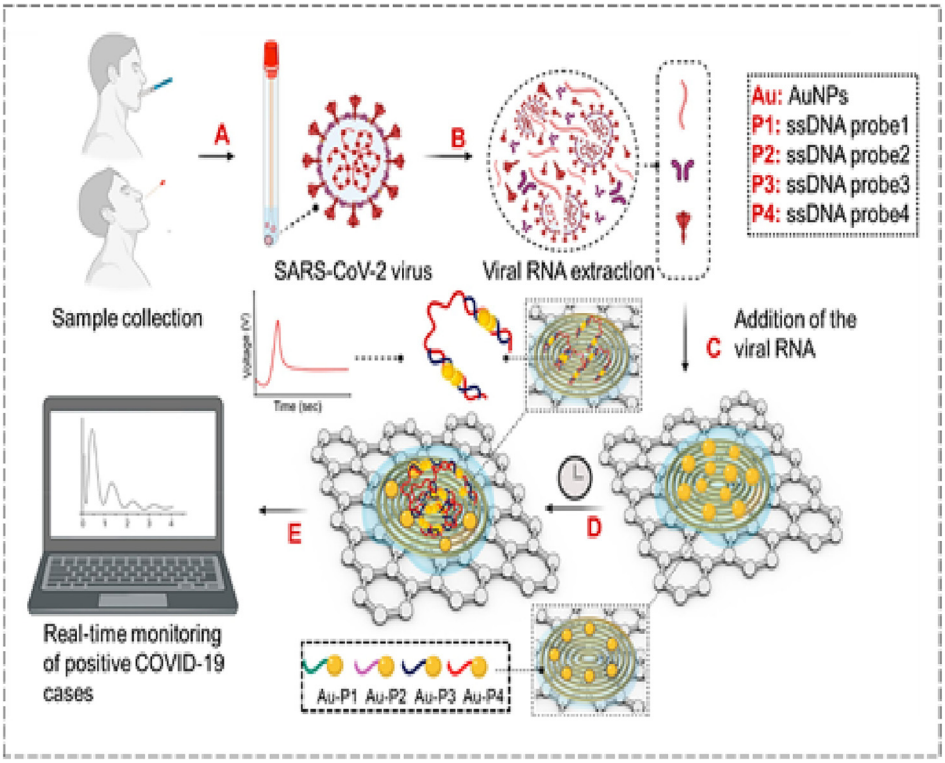

Fig. 6. Illustrate of the SARS-COV-2 variant electrochemical sensors instrument: A. Infected samples are collected from nasal swabs or patient saliva under observation, B. SARS-CoV-2 RNA is extracted, C. Viral RNA is added to graphene-ssDNA-AuNP, D. Incubation is allowed for 5 min, and E. Electrochemical output is recorded digitally. Reprinted with permission of Alafeef et al. (2020), Copyright 2020, ACS Nano.

detection of SARS-CoV-2 was at levels as low as 82 copies with this modified test. In particular, it made it possible to precisely differentiate a crucial mutation of the SARS-CoV-2 variation called D614G, which can cause a greater risk of epidemic and pathogenetic spread (Wang et al., 2021). Present an amplification-free CRISPR-Cas13aassay to directly detect SARS-CoV-2 from nasal swab RNA using a mobile phone microscope. The test achieved a sensitivity of 100 copies/ml in <30 min after identifying reextracted RNA from a panel of positive clinical samples in <5 min. The method combines crRNAs targeting SARS-CoV-2 RNA to increase sensitivity and specificity by measuring viral load using enzyme kinetics (Fozouni et al., 2021). Researchers have developed a fully automated CRISPR-LAMP platform that can manipulate droplets and perform combined reactions with high sensitivity and specificity, detecting SARS-CoV-2 mutations with a detection limit of 102 copies/μl (Zhang et al., 2022). Fig. 7 shows the compact CRISPR-Cas13a system integrated into mobile phone microscopes, as well as the design of mobile phone microscopes that detect fluorescence. CRISPR-Cas13a is a gene editing tool for the detection of RNA. The compact system consists of Cas13a enzymes and guide RNAs that specifically target and separate the interesting RNA sequences, such as SARS-CoV-2. The system is designed to generate fluorescent signals when targeting RNA is cut, and can be detected with the help of mobile phone microscopes (Table 1).

3.5. Smartphone-based biosensors for at-home testing

This section discusses the development of smartphone-compatible biosensors. These biosensors utilize the smartphone's camera and other sensors to perform various tests, such as identifying the presence of certain chemicals or pathogens in a sample highlights the most recent innovations in smartphone-based biosensors and their potential for detection SARS-CoV-2 variants. A diagnostic device called SHERLOCK-minimally instrumented (miSHERLOCK) was developed by scientists at the Harvard University Wyss Institute for Biologically Inspired Engineering, the Massachusetts Institute of Technology. Diagnostic tool for treating patients using natural saliva to extract, purify, and concentrate viral RNA. Performs amplifier and detection reactions, delivers fluorescent visual output in 1 h, and requires only three user actions (Madrid et al., 2022). Furthermore, it can be quickly adjusted to identify different viruses and SARS-CoV-2 and mutations associated with variants B.1.1.7, B.1.351 and P.1 by multiplication of compassion. An optional smartphone app allows for output quantification, automatic interpretation, and the potential for remote, dispersed result reporting, producing data that can be read and validated by an accompanying smartphone application in a matter of hours (De Puig et al., 2021), as shown in Fig. 8-A. A study provides home testing, and a POC called "Harmony COVID-19" was created using low-cost consumables, prefilled reagents, and straightforward equipment. The method develops a multiplexed reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay that can report results in as little as 17 min for samples with a high viral load (5000 copies/ml) using a nasal matrix or saliva sample containing 0.5 virus particles/l; Harmony was able to detect 97 or 83 % of the simulated models (Panpradist et al., 2021). A smartphone uses a loop-mediated isotopic amplification assay to detect SARS-CoV-2 and influenza. The method tested two groups of 20 individuals with symptoms in positive symptomatic SARS-CoV-2, and the SARS-CoV-2 screening tests at admission were negative for 30 asymptomatic members of the same population. However, this study had some limitations that required more participants (Heithoff et al., 2022). COVID-19 patient monitoring system using quantum barcodes on smartphones have also been evaluated. Compared to lateral flow tests, its technology was 90 % more sensitive and 100 % more specific for SARS-CoV-2. The corresponding values for the lateral flow assays were 34 % and 100 %, respectively, (Zhang et al., 2021), as shown in Fig. 8-B. Biosensors and characterization methods have tremendous potential due to their wide use and educational benefits. However, biological and chemical sensors face scientific challenges before providing reliable, accurate, and early disease detection in four primary categories of split virus detection: First, direct viral diagnosis: A perfect virus can only be detected by biosensors or, more generally, by cell culture methods (Caygill et al., 2010). Establish a saliva-based SARS-CoV-2 reverse transcription loop-mediated isothermal amplification (RT-LAMP) system. A

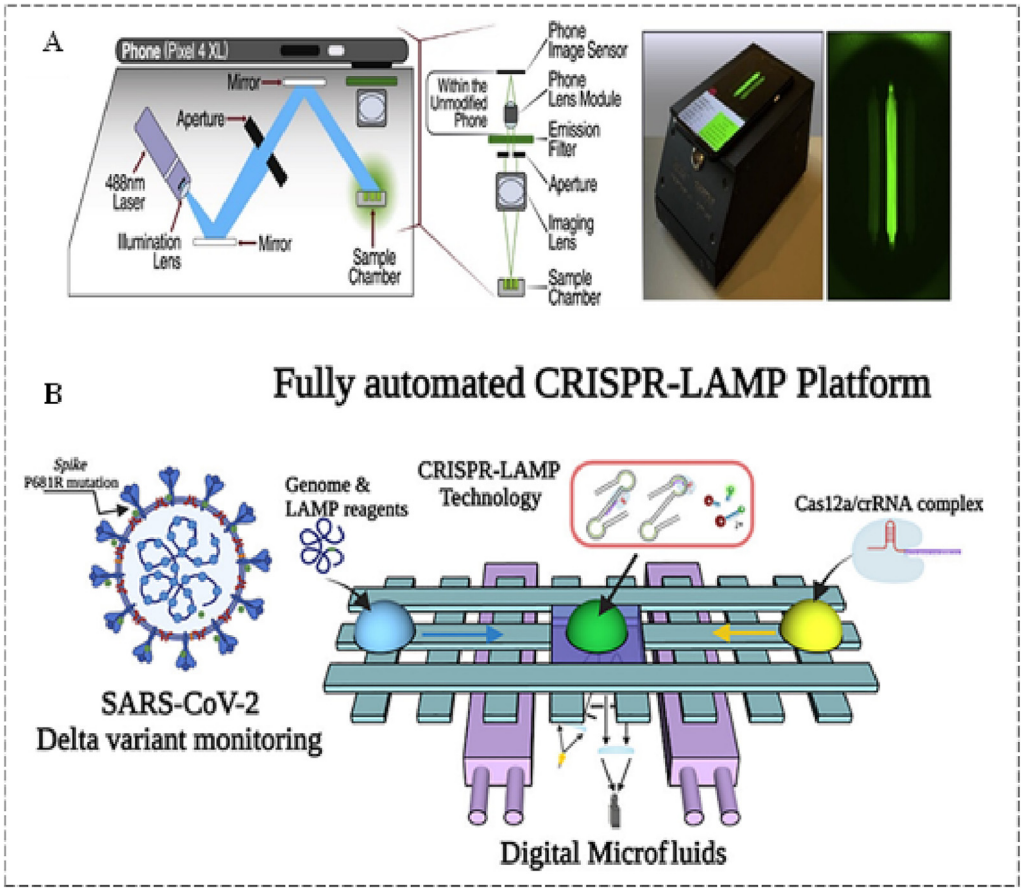

Fig. 7. Detection of SARS-COV-2 variants based on CRISPR: A. Mobile phone-based microscope for fluorescence detection and images of CRISPR-Cas13a-based mobile phone microscopy. Reprinted with permission of Fozouni et al. (2021), Copyright 2021, Cell. B. CRISPR-LAMP platform that is automated, Reprinted with permission of Zhang et al. (2022), Copyright 2022, Analytical Chemistry.

platform handles everything from preparing viral particles by thermal lysis to sample dispensing, from target sequence RT-LAMP amplification to the result from reporting and communication. The results can identify in LoD 5 copies/μl of saliva with a turnaround time of <45 min (Tang et al., 2022).

4. Challenges and opportunities

In its early stages, COVID-19 diagnosis is based on clinical symptoms and interactions with potentially infected individuals. However, the clinical symptoms and signs are inconclusive, thus requiring further diagnostic and serological tests (Filipić et al., 2020; Liu et al., 2020). Low- and middle-income nations bear the majority of the disease burden due to a lack of laboratory capacity for diagnosis, treatment, and care of current diseases and new infections (Bandawe et al., 2022; Vitoria et al., 2009). Developed molecular diagnostic tests based on RT-qPCR for detecting SARS-CoV-2 are available, but their usage in resource-poor areas is challenging due to the need for specialized personnel and equipment. SARS-CoV-2 detection methods are becoming increasingly sophisticated as research progresses, and new mutant viruses require periodic validation of testing procedures for both sensitivity and specificity (Wei et al., 2023; World Health Organization, 2020). Further information on these new infections and their control is expected to become available as viral genome sequencing and research progress, along with innovative vaccination techniques (Ramachandran et al., 2020).

Many systemic challenges associated with laboratory systems exist in low- and middle-income countries, including a lack of laboratory supplies, equipment, skilled personnel, educators, and training programs, insufficient logistic support, a de-emphasis on laboratory testing, inadequate testing quality monitoring, decentralization of laboratory facilities, and a lack of government laboratory standard (Petti et al., 2006; Shen et al., 2021; Arya et al., 2019). The efficiency and accuracy of detection methods depend heavily on the quality of samples used, such as throat swabs, nasal swabs, deep throat saliva, and sputum samples collected from the upper and lower respiratory systems (Oh et al., 2021; Luka et al., 2015). The logistics of collecting and transporting samples to a lab are crucial to making an accurate diagnosis, and misidentification due to sample contamination, poor sample collection, handling, transportation, or storage, insufficient samples, or the presence of interfering chemicals may contribute to diagnostic errors. Preparing the workforce for new responsibilities could lower the number of required workers and redirect the focus on activities that add value, such as quality evaluation and the implementation of new diagnostic tests (Lippi and Da Rin, 2019; Yu et al., 2020; Lin et al., 2020) Therefore, A sophisticated network of nanophotonic biosensors can monitor virus mutations to enhance healthcare quality. Limitations of biosensors in detecting SARS-COV-2 mutations are presented in Table 2.

5. Advancements in nanophotonic-based biosensors for SARS-CoV-2 variants detection

Today, nanophotonic biosensors are capable of a wide detection range of pathogens/diseases (Chaudhary et al., 2022c, 2023c). Typically, a suitable capture reagent is all that is required. Although larger molecules, such as antibodies and enzymes, are recognized by these sensors, smaller molecules, such as metabolites, are difficult to detect (Yoo and Lee, 2016; Chaudhary et al., 2022b). However, this variation still allows for a great deal of versatility in use. Even though it is still in its infancy, many scientists are already planning for the promising future of the field of point-of-care nanophotonic. Real-time tracking of essential biomarkers is being

Table 1
Analysis and summary of the latest innovations techniques for detecting the SARS-CoV-2 virus and its variants.

Instruments/year	Target	Variant detection	LOD	Duration	Sample	Sensitivity	Application	Ref
Photonics nanosensor (2022)	SARS-CoV-2	✓	598 FFU ml^{-1}	$^{<}$20 min	RBD	97 %	Hospitals and laboratories	(Ruiz-Vega et al., 2022)
Microfluidic (2022)	SARS-CoV-2	✓	57.8 ng/ml	20 min	Antibody levels	46.67 %	POC test	(Wu et al., 2022)
SERS (2021)	SARS-CoV-2	✓	300 nM	Na	ACE2 and RBD	NA	On-site and POC test	(Payne et al., 2021)
SPR with large gold (AuNPs) (2022)	SARS-CoV-2	✓	85 f. (4 pg/ml)	15 min.	Nucleocapsid protein	NA	POC test	(Yano et al., 2022)
Optical imaging spectroscopy (2022)	SARS-CoV-2	✓	10^2–10^6 copies ml^{-1}	54 patients in 300 S	Spike protein	100 %	POC test	(Gomez-Gonzalez et al., 2022)
Colorimetric (2021)	SARS-CoV-2	✓	0.154 pg ml^{-1}	5 min	ACE2	96 %	POC test	(Ferreira et al., 2021)
RT-LAMP assay with multi fluorescent probes (2022)	SARS-CoV-2	✓	20 and 2 copies/μl	NA	RNA protein, ORF1ab, and N gene	0.9915 and 0.9956	Clinical settings in resource-limited regions	(Talap et al., 2022)
Graphene FET sensor (2021)	Screening of COVID-19	✓	0.03 copy μl^{-1}	~1 min	RNA protein, ORF1ab, and N gene	$\sim 1.3 \times 10^{-4}$ and $\sim 3.4 \times 10^{-5}$ mV	On-site and POC test	(Kong et al., 2021)
FET sensor (2022)	SARS-CoV-2	✓	100 pg ml^{-1}	20 min	ACE2, Spike, and antibody	~165 copies/ml	Screening of infectious diseases	(Park et al., 2022)
Electronic sensor/BioScreen (2022)	SARS-CoV-2	✓	0.1 ml	21 min	Spike S1, G antigen, blood serum, and swab	99.2 %	Point of care	(Macchia et al., 2022)
Electrochemical (2021)	SARS-CoV-2	✓	229 fg ml^{-1}	6.5 min	ACE2	100.0 %	POC test and population surveillance	(de Lima et al., 2021)
Electrochemical (2021)	SARS-CoV-2	✓	2.8 fg ml^{-1}	4 min	ACE2	100 %	POC test	(Torres et al., 2021)
Electrochemical chip (2020)	SARS-CoV-2	✓	6.9 copies/μl	$^{>}$5 min	RNA and N-gene	231 (copies $\mu l^{-1})^{-1}$	POC test	(Alafeef et al., 2020)
CRISPR-Cas13 (2021)	MERS, SARS-CoV and SARS-CoV-2	✓	82 copies	20 min	RNA and D614G	NA	Monitoring Clinical	(Wang et al., 2021)
CRISPR-Cas13 with mobile phone (2021)	SARS-CoV-2	✓	100 nM	$^{>}$5 min	RNA	~100 copies/μml	POC test	(Fozouni et al., 2021)
CRISPR-LAMP platform (2021)	SARS-CoV-2	✓	10^2 copies/μl	1 h	Spike, T478K, D614G, P681R, and P681H	100 %	Clinical diagnostic	(Zhang et al., 2022)
Smart – phone miSHERLOCK (2022)	SARS-CoV-2	✓	100,000 cp/ml	55 min	RNA protein	2–20-Fold	Test at home and POC	(De Puig et al., 2021)
Harmony COVID-19 KIT with smartphone (2021)	SARS-CoV-2	×	0.5–2.5 copies/μl	17 min	RNA protein	95 %	Test at home and POC	(Panpradist et al., 2021)
Smartphone-based LAMP (2022)	SARS-CoV-2/influenza	✓	10^3 copies/ml	25 min	variant gRNAs	100 %	POC	(Heithoff et al., 2022)
Smartphone using Quantum dot (2021)	SARS-CoV-2	✓	1.99 & 0.11 pM	Real-time	RBD and N-gene	90 %	Healthcare system	(Zhang et al., 2021)
RT-LAMP based on smartphone (2022)	SARS-CoV-2	✓	6 copies/μl	45 min	Nucleic acid, sequence	NA	Test at home	(Tang et al., 2022)

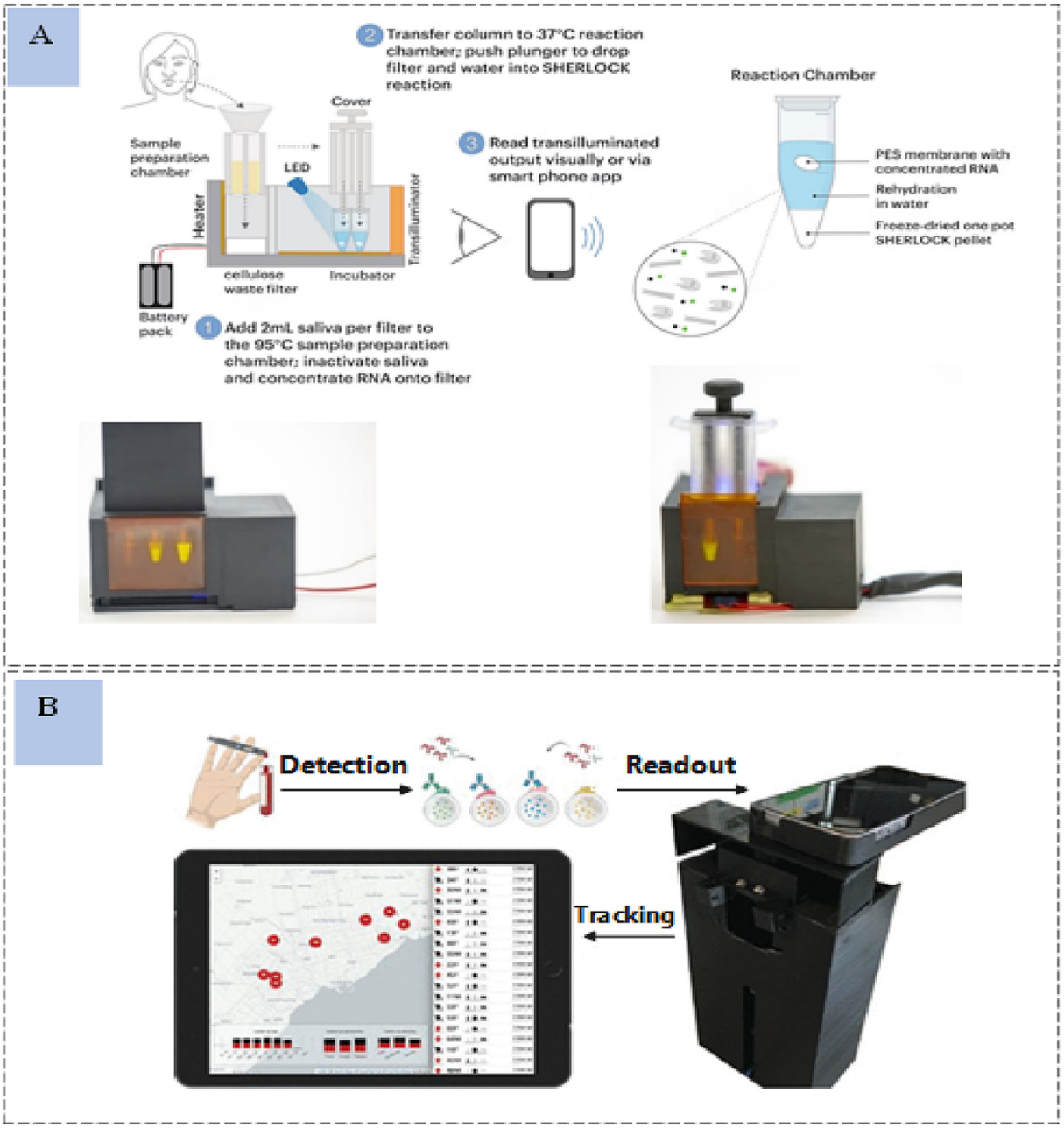

Fig. 8. Portable variants of the SARS-COV-2 virus tested based on the smart phone: A. MiSHERLOCK schematic showing the integration of instrument-free viral RNA extraction and concentration from raw saliva, reactions that identify SARS-CoV-2 and variations, fluorescence output and an auxiliary mobile phone app for automatic result interpretation. Reprinted with permission of De Puig et al. (2021), Copyright 2021, Science Advances. B. Smartphone-based imaging device for quantum dot barcodes scan immunoassay. Reprinted with permission from Zhang et al. (2021), Copyright 2021, ACS Nano Letters.

investigated for its potential with implanted and wearable nanophotonic devices (Guo et al., 2021). Additionally, there are still significant obstacles to overcome, since light delivery within the body is problematic and the body has a natural predisposition to reject alien objects (Kwon, 2022). The Mexican Optical Research Center is developing wearable sensors incorporated in nanophotonic materials, including gold (Gao et al., 2019). This paper proposes a new family of 3D nanophotonic structures inspired by general relativity, in which light is subjected to the curvature of the medium as it evolves. Wave packets traveling through our curved-space structure can have their trajectories, diffraction characteristics, phase, and group velocities manipulated to our liking (Bekenstein et al., 2017). Nanophotonic biosensors with improved compactness, portability, and throughput are enabled by integrated photonic circuits. Integration strategies can be classified as vertical or planar. Nanostructures can be used in vertical integration to reduce optical coupling requirements, eliminating the need for external optical couplers such as prisms, gratings, or waveguides. The use of collinear light can efficiently miniaturize and multiplex nanostructures, resulting in high multiplexing limited only by the diffraction limits of light (Lopez et al., 2017; Zanchetta et al., 2017; Taha et al., 2022). Optical waveguides can be arranged in a 1D array and functionalized separately for multiplexed detection in planar integration approaches. Sensor chips can be further miniaturized by hybridizing the optoelectronic components and the electronics layer. Commercially viable silicon-based integrated sensors using conventional waveguides and optical microresonators such as micro rings and photonic crystal cavities are used in most planar sensors (Hu et al., 2019; Lee et al., 2019). However, to analyze extremely absorptive or turbid solutions, one must consider the effects of optical loss, interference, and scattering, which might occur because

Table 2
A summary of biosensor challenges for the detection of SARS-COV-2 variants.

Biosensor categories	Challenges
Optical biosensor	• The variability of SARS-CoV-2 variants can affect biosensors' sensitivity and specificity. • False positive findings can occur due to cross-reactivity with other viruses or non-specific binding to non-target molecules. • Surface functionalization and immobilization optimized for each variant to ensure efficient and specific binding of target molecules. • The preparation and handling of samples can be complicated and time-consuming, which requires specialized personnel and equipment.
Electronic biosensors	• The sensitivity and specificity of biosensors to detect new viral strains are limited. • Need for regular updates and modifications of biosensors to keep pace with the evolving virus. • Lack of standard protocols for collecting and processing samples, resulting in inconsistent results.
Electrochemical biosensors	• Need sensitive electrodes to detect low viral loads. • Biological samples' severe circumstances can alter the sensor's electrode material, decreasing sensitivity and specificity. • Cost can be a challenge to widespread adoption, especially in areas with limited resources.
CRISPR biosensors	• Require RNA sequences to bind to Cas proteins, making high specificity difficult. • RNA sequences that are similar can cause false positives • Limited in their ability to detect multiple targets simultaneously. • The CRISPR biosensor must be administered to the respiratory tract in a steady and effective way.
Smartphone-based biosensors	• Limited sensitivity and specificity compared to laboratory--based assays • Limited capability for multiplexed detection of multiple targets. • Dependence on smartphone camera quality and lighting conditions • Need to optimize and validate different smartphone models and operating systems

light must travel through the sample during vertical integration. Individual sensing components often use nanostructure arrays to provide a more excellent output signal than individual particles in practice. This set of parts may be configured in 2D arrays for multiplexed detection (Wang et al., 2020; Mudumba et al., 2017; Chaudhary et al., 2023c). Future work on nanophotonic biosensors for SARS-CoV-2 detection can improve sensor sensitivity and specificity, and increase their multiplexing capabilities. Researchers can also explore the use of different types of nanostructures and materials for biosensor applications and new integration strategies for smaller and more portable devices (Vaisocherová et al., 2015; Maan et al., 2020; Yoo et al., 2015; Galloway et al., 2013).

5.1. Nanophononics units

Nanophotonic units are subwavelength optical devices that can operate light and manipulate light at the nanoscale, which typically involves structures with dimensions smaller than the wavelength of light. These units consist of various nanoscale components, such as waveguides, resonances, and optical cavities, which limit and control light diffusion. Controls the properties of light, such as its intensity, polarization, phase, and propagation direction, via nanoscale materials and electronics (Tran et al., 2022). Nanophotonics can be utilized to increase the sensitivity and selectivity of optical biosensors by taking advantage of the small interaction between light and biomolecules and can accomplish this by creating nanophotonic structures capable of confining and amplifying the electromagnetic field around the sensor region, enabling more efficient biomolecular interaction detection (Prasad, 2004; Koenderink et al., 2015). A 2D photonic crystal waveguide, coupled to resonant cavities, can serve as a wavelength division multiplexer in optical communications. This waveguide is made of dielectric materials with different refractive indices, creating a photonic bandgap that restricts specific wavelengths of light. As a result, light with certain wavelengths can be trapped in resonant cavities and sent through a waveguide to different output ports. This technology has potential applications in high-speed optical communications and optical sensing (Akahane et al., 2003). A plasmonic dimer nanoantenna coupled to an optical emitter is a structure that can produce directional light emission. It consists of two closely spaced metallic nanoparticles supporting plasmon resonances and an optical emitter emitting light when excited. The plasmon resonances can enhance the emission of light from the emitter and direct it in the desired direction. This technology has potential applications in imaging, sensing, and optical communication systems. However, careful design and experimental characterization are necessary for optimal performance due to various factors affecting the structure (Netherton et al., 2022). A metasurface made of chiral antennas selectively interacts with circularly polarized light by modifying the phase and amplitude of its left- and right-circularly polarized components. Furthermore, this creates a chiral filter discriminating between the two polarizations with optical communication, spectroscopy, and biological imaging applications. Chiral metasurface design and fabrication can be challenging, but recent nanofabrication advances have opened up new research possibilities (Lee et al., 2014). The metal-insulator-metal (MIM) surface plasmon polariton (SPP) waveguide can confine light and reduce its wavelength at the nanoscale. It comprises a metal layer between two insulator layers with a nanoscale gap. When light is coupled into the waveguide, surface plasmon polaritons can be excited, leading to strong confinement of the light and a reduction of its wavelength. This technology has potential applications in nanophotonics, sensing, and optical communication systems that must consider limitations such as propagation length and losses (Bidault et al., 2019).

5.2. Nanophotonics enabling artificial neural networks

The unique properties of photons could solve some of the problems electronics face. For example, photons are helpful as information carriers because they have high speeds of propagation, low chances of interference, and many parallelisms. In addition, nanophotonics enable signal multiplexing over time, space, polarization, angular momentum, and wavelength. As a result, optical waveguides or fibers have replaced copper connections in computer processors and data centers, due to the development of optical interconnect technology (Deng and Liu, 2014; Ren et al., 2016; X. Li et al., 2015; Deng et al., 2015). Consequently, artificial neural networks (ANNs) are computational systems that are inspired by the structure and function of biological neural networks in the human brain. ANNs are made up of interconnected nodes that can process and transmit information. Recently, researchers have started exploring the use of nanophotonics to enable ANNs with improved performance and energy efficiency (Appeltant et al., 2011). Nanophotonics also allows for the development of compact and efficient ANNs. By using nanoscale photonic components, such as waveguides and photonic crystals, ANNs can be integrated into small form factors, making them ideal for use in portable and wearable devices. One of the main advantages of using nanophotonics in ANN is the ability to perform parallel calculations. In traditional electronic ANNs, the computation is performed sequentially, which can cause bottlenecks and delays in processing. With nanophotonics, parallel computations can significantly improve processing speed and reduce energy consumption (Mesaritakis et al., 2016; Kaikhah and Loochan, 2001; Lin et al., 2018). Overall, the use of nanophotonics in ANNs holds great promise for the development of efficient and high-performance computing systems. However, many challenges remain to be overcome, such as the integration of nanophotonic components with existing electronic systems and the development of new fabrication techniques for nanophotonic devices. (Jones et al., 2019; M. Li et al., 2015; Owoicho et al., 2021)

5.3. Benefits of AI-enabled nano-photonic optical biosensors

The development of optical biosensors based on nanophotonics and artificial intelligence can be very useful in detecting SARS-CoV-2 variants. Some potential applications are: Rapid screening of SARS-CoV-2 variants:

- **Rapid screening of SARS-CoV-2 variants**: Optical biosensors can be used to detect specific mutations or SARS-CoV-2 variants with specific probes or antibodies. Using nanophotonic structures improves the sensitivity and specificity of biosensors, and AI algorithms help detect and classify different variations.
- **Monitoring of viral loads and replication**: optical biosensors can be used to monitor the viral load and replication of SARS-CoV-2 in patient samples and provide feedback on the effectiveness of antiviral treatment in real time. Nanophotonic structures can detect low viral loads and artificial intelligence algorithms can help analyze and interpret sensor data.
- **Environmental monitoring of SARS-CoV-2 variants**: Optical biosensors can be used to monitor SARS-CoV-2 variation in the environment, such as wastewater and air samples. Nanophotonic structures can improve the sensitivity of biosensors, while artificial intelligence algorithms can help detect and track different variants.
- **SARS-CoV-2 Point of Care Diagnostics**: Optical biosensors can be designed as portable and easy-to-use devices for SARS-CoV-2 Point of Care Diagnostics. The use of nanophotonic structures can allow biosensors to be miniaturized and integrated, while artificial intelligence algorithms can analyze and interpret sensor data in real time. Overall, the combination of nanophotonic structures and AI algorithms may lead to the development of highly sensitive, selective and efficient optical biosensors for the detection of SARS-CoV-2 variants and have potential applications in the field of clinical, environmental and public health.

Fig. 9 shows integrated nanophotonic biosensors that are the future of artificial intelligence for multiattribute decision support systems to detect analytes in different environments. This integration represents a promising avenue for future applications of nanophotonics biosensors in analyte detection.

6. Conclusions

The outbreak of coronavirus diseases has had a significant impact on human life and economic development. SARS-CoV-2 continues to mutate during transmission, making epidemic control and prevention more complex and potentially reducing the effectiveness of the vaccine. The severity of the disease has decreased due to vaccinations and virus mutations and may coexist with humans in the future. Clinicians have faced significant challenges in quickly identifying microorganisms and pathogens, but validated technologies such as optical biosensors and photonics have been developed in microbiology laboratories to decrease the time required to detect viruses in a few minutes. This advancement in technology also addresses the decreasing number of experienced laboratory personnel and makes patient care more cost-effective and efficient by automating tasks. Technician responsibilities will shift from manual handling to handling sophisticated instruments in the future. Automation also helps to alleviate the strain caused by the growing backlog of test samples and the shrinking workforce of microbiologists. By combining cutting-edge biological technologies with intelligent image analysis, non-productive workflow disruptions can be eliminated and the microbiologist's time can be freed up for more valuable tasks like result interpretation and client counseling. In summary, AI-powered laser-assisted diagnosis can improve food safety inspections, air virus density analysis, and environmental monitoring. An intelligent optical network of medical biosensors can also improve healthcare quality by collecting information for virus detection using an optical network linked to a multi-intelligent microbiology laboratory.

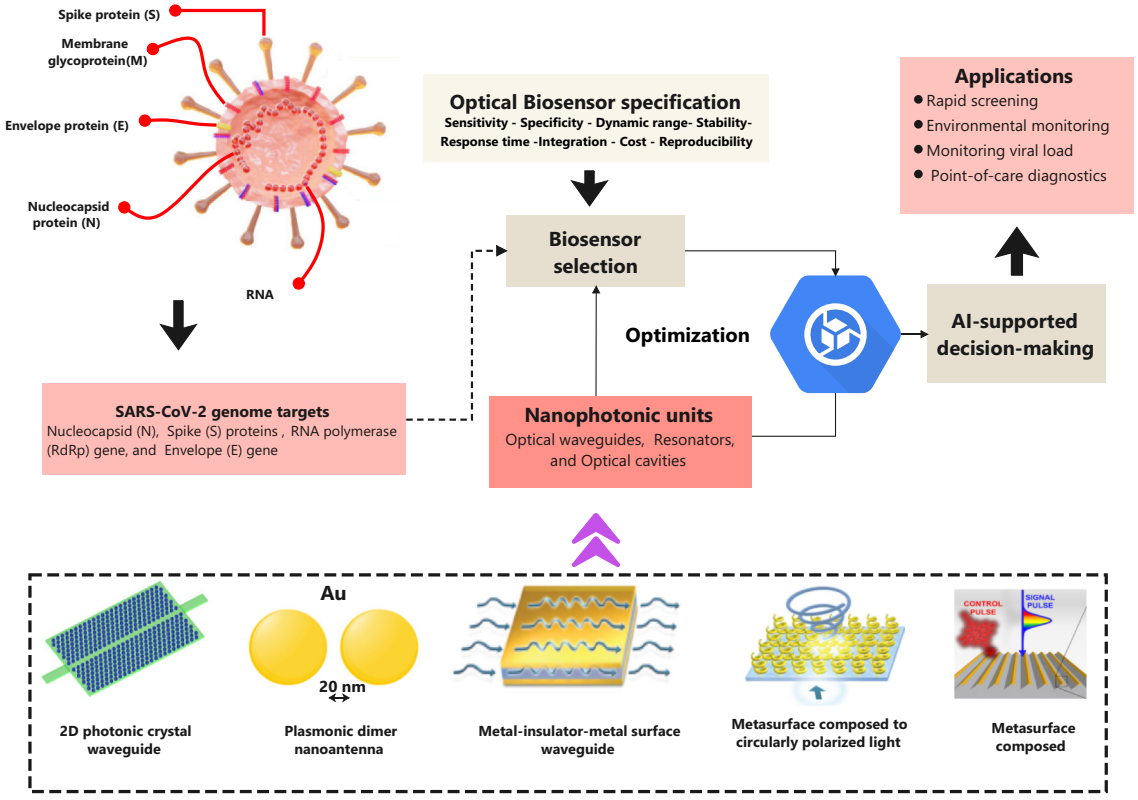

Fig. 9. Showcases the potential of integrated nanophotonics biosensors and artificial intelligence (AI) for creating multi-attribute decision support systems capable of detecting analytes in diverse environments.

Abbreviations

COVID-19	coronavirus disease
SARS-CoV-2	Coronavirus Severe Acute Respiratory Syndrome 2
TEM	Transmission Electron Microscopy
ACE2	angiotensin-converting enzyme 2
HR	Heptad Repeat
SLIC	Simple Linear Iterative Clustering
SARS-COV	Severe Acute Respiratory Syndrome Coronavirus
RSIs	Receptor-Specific Interactions
hACE2	higher angiotensin-converting enzyme 2
RBD	receptor-binding domain
BNNs	biological neural networks
λ	wavelength

CRediT authorship contribution statement

B.A.T., wrote the initial manuscript draft, Conceptualization and methodology, Y.A.M., investigation, Conceptualization and methodology, Q.A., Writing - Review & Editing., N.A., supervision and validation., Formal analysis and resources., Y.L., Validation., Z.C. & S.R., Writing - Review & Editing., and V.C., Writing - Review & Editing. All authors have reviewed and accepted the published version of the manuscript.

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Data availability

Data availability is available on GISAID: (https://www.gisaid.org/) and (https://ourworldindata.org/).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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