

Section IV: Applications of Sensor Technologies in Virus Detection

CHAPTER 12

Point of Care Diagnostics for Virus Detection

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12.1 Introduction

Infections caused by viruses are responsible for millions of deaths that occur every year around the globe.¹ In situations when there is no vaccination that has been proven to be successful, the public health approach is to make an early diagnosis in order to either place those who may be sick under quarantine or recommend that they make changes to their lifestyle in order to avoid the spread of infection.² Centralized laboratory procedures, such as the enzyme-linked immunosorbent assay (ELISA) and the polymerase chain reaction (PCR), are currently the diagnostic methods that are considered to be the standards for the diagnosis of viral infections.³ Due to the fact that these methods require a considerable amount of time, they are not suitable for widespread implementation in nations where the health care systems are not sufficient to give adequate services to all of the population.⁴ Point-of-care (PoC)

diagnostics have been presented as a means of overcoming these disadvantages. If such diagnostics are successful, they have the potential to significantly enhance public health worldwide.⁵

Among the many benefits of PoC testing (PoCT) is adaptability to different stages of patient treatment. A hospital’s operating room, intensive care unit, or emergency room can all make use of it. Importantly, it can also be used in areas with low resources, in the community, as an outpatient environment, and in the home. The development of PoC devices has great potential for improving health monitoring and early disease identification, facilitating the transition to personalized treatment, and enhancing preventative care⁶ (Figure 12.1a). For PoC tests, a number of different physiological fluids (urine, tears, blood, saliva, or sweat) can be utilized.^{7–9} Electrolytes, hormones, and early indicators of infection are just a few of the many biomarkers that may be examined in these samples to track an individual’s health.

Affordable, sensitive, specific, user-friendly, rapid-robust, equipment-free, and deliverable to end-users are the ASSURED characteristics that the World Health Organization (WHO) uses to define the ideal PoC test¹⁰ (Figure 12.1b). Although numerous PoC technologies have been created for the diagnosis of viral infections in the last decades, the majority of them fall short of even near-PoC standards and do not meet the ASSURED requirements. Crucially, a test’s market competitiveness increases in direct proportion to how closely it matches the ASSURED standards. For example, out of all the PoC tests, approximately 20% are fully ASSURED-compliant lateral flow immunoassays.¹¹ However, regulatory considerations also play a role in determining a

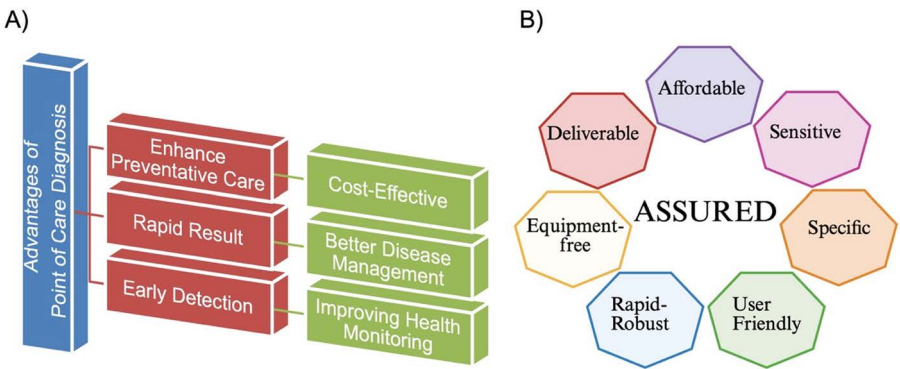


Figure 12.1 (a) Key advantages PoC diagnostics, including early detection, rapid results, enhanced preventative care, cost-effectiveness, better disease management, and improved health monitoring. (b) The ASSURED criteria defined by the WHO for ideal PoC diagnostics: affordable, sensitive, specific, user-friendly, rapid-robust, equipment-free, and deliverable. Created in BioRender. E. Yılmaz, 2025. <https://BioRender.com/xu5d72u>.

test's efficacy; for example, Australia's prohibition on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PoC tests.¹²

This chapter offers a thorough summary of the most recent developments in PoC diagnostics for virus detection. It begins by exploring the sensor technologies that form the foundation of PoC systems, including optical, electrochemical, and microfluidic-based biosensors. Then, with a focus on their function in identifying respiratory, sexually transmitted, blood-borne, vector-borne, and foodborne viruses, PoC diagnostic clinical uses are addressed. Finally, the chapter discusses the technical and legal issues confronting PoC technologies as well as future trends—such as the integration of artificial intelligence (AI), internet of things (IoT), and new materials—which are set to transform the sector. PoC technologies are poised to be crucial in fighting viral infections and enhancing worldwide health results by closing the gap between centralized laboratory testing and real-time, on-site diagnostics.

12.2 Sensor Technologies for PoC Virus Detection

Contagious pandemics, including H1N1, the Zika Virus, the SARS and Middle East respiratory syndrome (MERS) outbreaks, the Ebola virus outbreak, and most recently, coronavirus disease (COVID)-19, have significantly affected millions of people. Early detection of viral infections is essential to control the spread of the disease worldwide.¹³ The common conventional methods for virus detection are the real-time PCR (RT-PCR) assay, ELISA and the hemagglutination assay.¹⁴ Even though they are highly sensitive, they typically require a prolonged assay time and an expensive setup. The urgent need for a rapid, precise, and cost-effective diagnostic test for severe viral diseases to diagnose at the earlier stages and decrease the mortality rate has led to the development of PoC biosensor applications.

Biosensors are analytical tools utilized to measure biological components in diverse samples quantitatively or semi-quantitatively. Typically, there are three main segments in a biosensor that permit the detection of target elements: (i) a biorecognition molecule (antibody, molecularly imprinted polymer (MIP), aptamer, *etc.*), (ii) a transducer (optical, electrochemical, *etc.*), and (iii) signal processing. The initial biorecognition molecule attachment can be provided by a variety of techniques, such as physical methods (*e.g.*, entrapment, encapsulation, and adsorption) as well as chemical methods (*e.g.*, covalent bonding and cross-linking).¹⁵ The overall performance of the biosensor is significantly affected by the bioreceptor immobilization process and needs to be controlled to enhance the sensitivity and specificity of the system. Upon the adsorption of the target on the sensing substrate, binding events on the surface can be converted to readable output signals *via* transducers and can be measured. PoC sensing systems can be classified depending on the transducer type used, which is selected by considering the physicochemical changes during sensing.¹⁶

12.2.1 Optical PoC Biosensors

When light illuminates the material, there is an interaction, and different phenomena may be observed, such as reflection, absorption, and scattering.¹⁷ Fluorescence, luminescence, or plasmonic properties of the optic materials may be enhanced by altering certain features of the utilized material (size, aspect ratio, structure, *etc.*) and the light (wavelength, polarization, *etc.*). Optical biosensors quantify the alterations in the aforementioned features resulting from the binding of a target analyte to a detecting molecule immobilized on the surface of the optical sensor.

Plasmonic optical biosensor technology is a powerful diagnostic instrument that has become more widespread in the last decade.^{18,19} The virus detection process can be altered since plasmonic biosensors are highly versatile. For instance, the immobilized recognition element could be a monoclonal antibody [immunoglobulin M (IgM)],²⁰ PCR-amplified viral bodies,²¹ or DNA probes.²² One of the most common plasmonic optical biosensors is surface plasmon resonance (SPR), which quantitatively assesses binding events in real time without the need to tag the interacting molecules.²³ It sensitively quantifies the alterations in the refractive index resulting from molecular interactions at the sensor surface. It has been reported that Ebola viruses (EBOV) have been detected in real-time and without labels *via* SPR with a limit of detection (LOD) of 0.5 pg ml^{-1} .²⁴ RNA, receptor binding domain (RBD) glycoprotein, and immunoglobulin G (IgG) protein associated with the COVID-19 virus has also been screened with SPR.^{25,26} The SPR techniques can be tuned and confined around nanostructures fabricated on the optical surface, depending on their size and morphology; this phenomenon is termed localized surface plasmon resonance (LSPR). A nanoantenna-based biosensor has been developed that effectively identifies EBOV soluble glycoprotein (sGP) in human plasma at concentrations as low as 220 fg ml^{-1} , representing a remarkable 240 000-fold enhancement in sensitivity relative to the 53 ng ml^{-1} detection threshold of current EBOV immunoassays.²⁷ Another report described the development of an LSPR biosensor that utilizes silver nanostructures, produced through thermal annealing of thin silver films, to detect the dengue non-structural protein 1 (NS1) antigen, which can be identified early in the infection process. The biosensor incorporates blood-plasma separation to create a compact PoC lab-on-chip device that enables quick diagnosis in a total of 30 minutes of dengue NS1 antigen from $10 \text{ }\mu\text{l}$ of whole blood.²⁸ Different human immunodeficiency virus (HIV) subtypes (A, B, C, D, E, G, and subtype panel) were captured and detected in another nanoplasmonic integrated platform with 98 ± 39 copies per ml sensitivity in approximately 70 minutes from HIV subtype spiked whole blood samples (Figure 12.2a and b).²⁹ The second plasmonic optical biosensor type is Raman spectroscopy, which can be described as a method employed to determine molecular structure by examining the vibrational frequencies of bonds through the analysis of light scattered from the sample.³⁰ The low inelastic scattering of biological materials constrains the efficacy of conventional

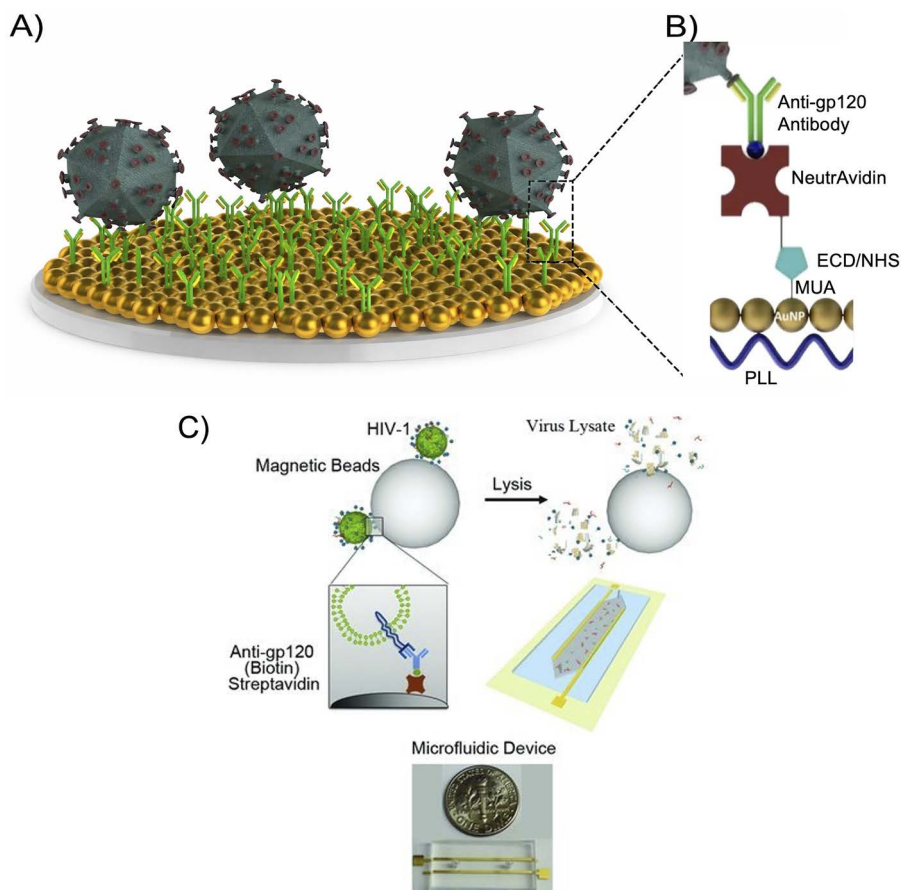


Figure 12.2 (a) Antibody immobilized nanoplasmonic surface and (b) the surface chemistry applications illustrated for HIV detection. Abbreviations: *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), 11-mercaptoundecanoic acid (MUA), *N*-hydroxysulfosuccinimide (NHS), gold nanoparticle (AuNP), poly-L-lysine (PLL). Reproduced from ref. 29 with permission from American Chemical Society Copyright, 2013. (c) Impedance-based HIV detection *via* a microfluidic PoC device is illustrated. Reproduced from ref. 50 with permission from John Wiley & Sons, Copyright 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Raman spectroscopy for sensitive virus detection due to insufficient signal strength. Further methods are required for signal amplification for more sensitive Raman signal detection. The plasmonic nanostructure-modified version of the system, known as surface-enhanced Raman spectroscopy (SERS), can magnify the signal intensity by over one million times and enable up to single-molecule detection.³¹ Additionally, SERS offers numerous advantages

over conventional Raman spectroscopy for virus detection, including (i) non-destructive analysis, (ii) reduced sample requirements, (iii) compatibility with liquid-phase sample measurements, (iv) multi-channel detection capabilities, and (v) the feasibility of on-site analysis using portable instruments.³² In the literature regarding the detection of various virus types, including SARS-CoV-2,³³ influenza³⁴ and respiratory infection virus (RIV),³⁵ Raman-based approaches, particularly the SERS method, have demonstrated significant potential for reliable viral identification with satisfactory LOD values.

Photonic crystals (PC) are also emerging technologies for biosensing applications, which can be defined as periodic configurations of uniformly formed materials with varying dielectric constants. Periodicity might vary as one-dimensional (1D), two-dimensional (2D), or three-dimensional (3D). PCs typically have specific colours owing to their unique wavelengths of reflection, which can be defined by the distance between layers. Alteration of the crystal's periodicity, such as through biochemical stimulation, will result in a corresponding shift in the wavelength of the reflected light.³⁶ Therefore, the PC effect provides the basis for practical instruments for biosensing applications. PC platforms can be fabricated by inexpensive methods and be used with complex media (such as urine, blood, sweat, *etc.*).³⁷ PC results are also easily accessible for visual interpretation by untrained operators. Furthermore, the procedures are expected to be cost-effective, and the handling process is rather straightforward. A label-free optical detection approach employing nanostructured PC for capturing and quantifying HIV-1 viruses from physiologically relevant samples was demonstrated in a study.³⁸ It was noted that surface-adsorbed biotargets caused a shift in the resonant peak wavelength value (PWV), which may be detected with a resolution of less than 10 pm, facilitating the identification of both biomolecular layers and a limited number of viruses that are poorly distributed on the transducer surface. The successful collection and detection of HIV-1 in serum and phosphate-buffered saline (PBS) samples with virus loads between 10^4 and 10^8 copies per ml were noted.

Fluorescent and colourimetric optical methods serve as alternative techniques for the detection and visualization of biomolecules owing to their high sensitivity, selectivity, rapid response, practical fabrication, ease of operation, and stability.³⁹ In a study, the sensing surfaces of zeolitic imidazolate frameworks (ZIFs) were modified with single-stranded DNA (ssDNA) to detect HIV with LOD as low as 1.2 nmol ml^{-1} . When probe ssDNA was bound to the target ssDNA on HIV, double-stranded DNA (dsDNA) formed, and the fluorescent signal increased.⁴⁰ In another study, the H5N1 avian influenza virus was detected by using a polydiacetylene-based colorimetric biosensor, which is a polymer that may switch colour from blue to red in response to external stimuli, such as mechanical stress. In the study, the H5 influenza virus was sensitively detected after binding to the recognition molecule with a detection limit of 0.53 copies per μl , exhibiting a pronounced blue-to-red

colour shift that is observable with the unaided eye or using a UV-visible spectrophotometer.⁴¹

12.2.2 Electrochemical PoC Biosensors

Electrochemistry is a fundamental analytical technique for observing reactions related to electron transfer. Electrochemical biosensors, which quantitatively measure the electron movements after the target and recognition element are bound, represent a prominent detection approach for numerous illnesses and demonstrate significant potential for PoC diagnostic applications owing to certain advantages. Rapid detection and data collection using electrochemical biosensors decreases the diagnosis time compared with conventional methods.⁴² They can reach high sensitivity and selectivity with miniaturized, portable, cost-effective and user-friendly structures.⁴³ When a viral target binds to the detection site, the reaction under investigation may produce measurable biochemical changes in: (i) the current (amperometric), (ii) the potential or charge accumulation (potentiometric), (iii) the voltage properties (voltammetric), or (iv) the impedance (resistance and capacitance) (impedimetric).⁴⁴

Amperometric measurement is an analytical method in which an applied voltage drives electrocatalytic redox reactions, producing measurable currents proportional to analyte concentration. A controlled-potential system is used, typically with a two- or three-electrode electrochemical cell, where one electrode serves as a reference. The working electrode facilitates the reaction, while the reference electrode (*e.g.*, Ag–AgCl or Hg–Hg₂Cl₂) maintains a constant potential. An auxiliary electrode (typically platinum or graphite) is also used. Erdem *et al.* utilized an amperometric disposable screen-printed carbon electrode (SPCE) for SARS-CoV-2 spike protein (S1) detection with an LOD of 0.19 ng ml⁻¹ in buffer and 0.13 ng ml⁻¹ in a saliva sample (10 µl volumes).⁴⁵ An anti-SARS-CoV-2 S1 monoclonal antibody was presented as the immobilized recognition molecule. The sandwich-type structure was established in the presence of the target S1 protein through the application of a secondary antibody and horseradish peroxidase (HRP)–IgG, respectively. 3,3',5,5'-Tetramethylbenzidine (TMB) was used as a mediator for oxidation/reduction, and quantitative amperometric measurements were recorded.

Potentiometric biosensors primarily measure voltage changes between electrodes and depend on a biological reaction that produces less complex ion compounds, which are then detected electrochemically (such as NH₄OH, CO₂, pH, H₂O₂, *etc.*).⁴⁶ The voltage fluctuation between a reference electrode and an indicator (measurement) electrode is detected using a high-impedance voltmeter, under conditions of nearly zero current flow in potentiometric biosensors. In a recent study, cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) measurements were conducted to detect potentiometric alterations of the Zika virus on a molecularly imprinted (MI) gold electrode.⁴⁷ Since antibody-based detection methods may result in false

positive results in other types of flaviviruses (in particular dengue virus), it was assessed that the MI method is a more selective detection method. The system detected 0.1 plaque forming units (PFU) ml^{-1} in buffer and 10 PFU ml^{-1} in human saliva samples that contained diverse biomolecules.

Voltammetric biosensors are another type that detect current in relation to the applied voltage, producing unique oxidation and reduction patterns related to the analyte. Voltammetry commonly employs techniques such as cyclic voltammetry, differential pulse voltammetry (DPV), and square wave voltammetry. They typically offer high selectivity with reduced cost and rapid analysis time. Abd Muain *et al.* have established a voltammetric immunosensor for the purpose of identification of Newcastle disease virus (NDV) utilizing polyclonal antibodies as the bioreceptor.⁴⁸ Antibodies were attached to a polyethylene glycol (PEG) self-assembled monolayer (SAM) surface. NDV was investigated electrochemically *via* DPV analysis, which presents an appealing alternative to standard detection methods owing to its simplicity, speed, and reduced labor requirements.

Finally, an impedimetric biosensor quantifies the impedance, defined as the resistance applied against the electrical current, of a system to indicate the presence or level of a target substance. Impedance is a combined measure of resistance, which opposes the flow of direct current, and reactance, which opposes the flow of alternating current. It can be affected by factors such as changes in the conductivity of the medium or the formation of biomolecular interactions on the surface of the sensor. In contrast to voltammetry and amperometry methods, which rely on direct current for measurements, EIS uses an alternating current potential or a sinusoidal signal applied to the electrochemical cell.⁴⁹ In an impedimetric sensor application study, a novel label-free approach, capable of detecting lysed viruses by impedance analysis was demonstrated (Figure 12.2c).⁵⁰ This method could be a feasible alternative to ELISA. It was evaluated with HIV-1 throughout a dynamic range of viral concentrations from 10^6 to 10^9 copies per ml; however, it was suggested that the system can be modified for other infectious disorders, including herpes, influenza, hepatitis, and poxes.

12.2.3 Microfluidics-based PoC Biosensors

To provide a comprehensive point-of-care system for viral detection, the previously described biosensors have typically been integrated with microfluidic devices in recent years. The most significant advantage of a microfluidic system is its small size, which permits reduced reagent volumes and portable devices with enhanced sensitivity. Recent advancements in portable microfluidic devices have increased their utilization, which has provided faster diagnostic studies and shortened analysis times.⁵¹ Considering these advantages, microfluidic on-chip sensors can be integrated with the aforementioned optical and electrochemical methods.^{45,50} Moreover, loop-mediated

isothermal amplification (LAMP) and reverse-transcription LAMP (RT-LAMP) techniques can be integrated into microfluidic systems for more efficient and compact testing of DNA and RNA viruses. LAMP and RT-LAMP are isothermal nucleic acid amplification methods that are alternatives to conventional PCR methods without the need for thermal cycling.⁵² In the literature, Zika, dengue (types 1 and 3) and chikungunya viruses have been reported to be detected with microfluidic PoC LAMP systems.^{53,54}

Paper-based microfluidics are a more cost-effective and easier alternative to conventional lithography-based microfluidic devices. Theillet and coworkers utilized a laser-cut microfluidic paper-based analytical device (PAD) to detect chikungunya virus from 30 μ l of patient serum.⁵⁵ The viral disease was detected in less than 10 minutes by the PAD with 70.6% sensitivity and 98% specificity, and the system showed reduced cross-reaction with other tropical viruses. Lateral flow assays (LFAs) are also practical tools characterized by their disposable design for determining the presence of an analyte. They are commonly used for PoC diagnostics, providing quick results with minimal equipment and technical expertise. During the COVID-19 pandemic, LFA strip applications provided significant help in diagnosis at the earlier stages.^{56,57}

12.3 Clinical Applications of PoC Diagnostics in Virus Detection

By allowing fast, precise, and easily accessible testing at or near the site of patient treatment, PoC diagnostics have changed the scene of virus detection. In clinical environments, these technologies are very important since they provide quick results that guide public health activities, infection control policies, and treatment decisions.⁵⁸ New PoC technologies have completely changed the way infectious disease viruses, particularly those preventable by vaccinations, are detected. Among the disadvantages of traditional laboratory procedures are slow turnaround times and inadequate sensitivity and specificity in response to new viral epidemics.^{59,60} These advancements in diagnostic tools seek to solve these problems. Examples of technological innovations include biosensors, clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated (Cas), and smartphone-enabled diagnostic tools.⁶¹ These technologies have changed significantly over time. Thanks to technological developments that have greatly improved patient outcomes, healthcare providers may now give patients accurate and fast results just when they need them. Molecular PoC testing now detects many viral infections, including respiratory, bloodborne, sexually transmitted diseases, vector-borne, and emerging viruses, as well as gastrointestinal and foodborne viruses. Every category has particular diagnostic difficulties; PoC technologies have been essential in removing these obstacles, therefore improving patient outcomes and facilitating disease management in several healthcare environments.⁶²

12.3.1 Respiratory Viruses

Respiratory infections are very common and can spread quickly, as seen with the COVID-19 pandemic. This can lead to major public health problems. In the last 20 years, respiratory viruses (RVs) such as SARS in 2003,⁶³ the influenza A virus (H1N1) in 2009,⁶⁴ and the MERS coronavirus (MERS-CoV)⁶⁵ in 2015 have caused major outbreaks that have had effects on society and the economy. The COVID-19 pandemic was the worst. It killed over 5 million people around the world by early 2022 and made it clear that the world requires better diagnosis tools right away.⁶⁶

The pandemic has made it clear how important PoC tests are for quickly treating respiratory virus infections. RVs like influenza, coronaviruses, respiratory syncytial virus, parainfluenza virus (PIV), adenovirus, rhinovirus, and other secondary viruses often have symptoms that are similar to each other, which makes it hard to make a correct diagnosis.^{60,67} PoC technologies have improved, allowing for faster infection diagnosis, more personalized treatment, and fewer complications.⁶⁸ They also help stop people from using too many antibiotics by identifying the difference between viral and bacterial illnesses.

In the absence of vaccines or antiviral medications, rapid and accurate diagnoses are of the highest priority in containing newly developing viruses. For the nucleocapsid (N) gene of MERS-CoV, a one-pot RT-LAMP approach was devised.⁶⁵ Within 60 minutes, this approach could identify as few as four viral genome copies using six primers and optimal enzyme conditions. For improved DNA polymerase compatibility, the EvaGreen dye outperformed SYBR Green I in signal read-out. Even more sensitive detection down to 0.4 viral genome copies was achieved using field-deployable microchamber devices, that did not exhibit cross-reactivity with other respiratory viruses, such as influenza A (H1N1, H3N2), influenza B, or human coronavirus 229E. Integrated into PoC equipment for quick, on-site detection, this sensitive and specific technology permits large-scale testing during emergencies (Figure 12.3a).

The current gold standard real-time quantitative PCR (RT-qPCR) method is one of the few SARS-CoV-2 detection methods that can identify two genes simultaneously, which is a critical step in improving detection accuracy. However, very few methods can achieve this. Xiong *et al.* presented a novel method for the quick and simultaneous detection of SARS-CoV-2 in a single strip test. It utilized a CRISPR-Cas9-mediated triple-line lateral flow assay (TL-LFA) in conjunction with multiplex reverse transcription-recombinase polymerase amplification (RT-RPA)⁶⁹ (Figure 12.3b). This test can identify 100 RNA copies per response ($25 \mu\text{l}^{-1}$) of SARS-CoV-2 viral RNA standards or cell-cultured SARS-CoV-2 using the envelope (E) and open reading frame 1ab (Orf1ab) genes. Also, analysis of 64 nasopharyngeal swab samples using dual-gene technology resulted in a near perfect score of 97.14 for positive predictive agreement and a perfect score of 100 for negative predictive agreement.

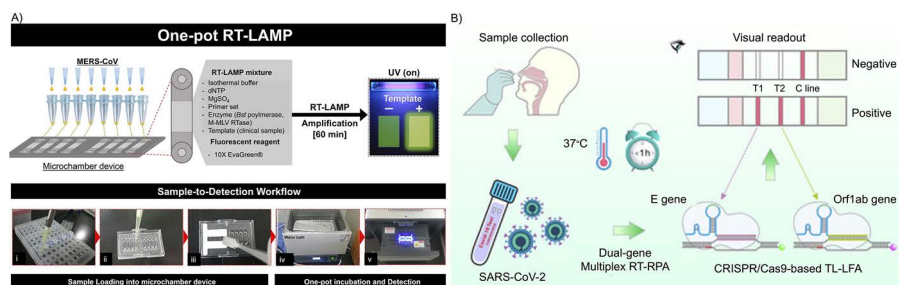


Figure 12.3 (a) The “sample-to-detection” scheme depicts the whole one-pot RT-loop-mediated isothermal amplification (RT-LAMP) process. (i)–(iii): Sample preparation and loading methods, (iv) and (v): One-pot incubation in water bath and LAMP signal read-out analysis. Reproduced from ref. 65, <https://doi.org/10.3389/fmicb.2016.02166>, under the terms of the CC BY 4.0 license, <https://creativecommons.org/licenses/by/4.0/> (B) A CRISPR–Cas9-mediated triple-line lateral flow assay combined with multiplex RT-RPA for simultaneous dual-gene diagnosis of SARS-CoV-2. Reproduced from ref. 69 with permission from John Wiley & Sons, Copyright 2020 Wiley-VCH GmbH.

Using this platform, people in areas with limited resources will have an easier and more precise way to diagnose infectious disorders like COVID-19.

12.3.2 Sexually Transmitted and Blood-borne Viruses

HIV, hepatitis B (HBV) and hepatitis C (HCV), human papillomavirus (HPV),⁷⁰ *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), syphilis, and *Trichomonas vaginalis*⁷¹ are among the sexually transmitted and blood-borne illnesses (STBBI) that remain significant public health issues. Because of the stigma and discrimination surrounding these diseases, which may deter people from getting tested and receiving treatment, STBBI are especially difficult to eradicate. Because of this, the general public have a low risk perception and a low acceptance rate of STBBI testing, and healthcare providers are reluctant to regularly give STBBI testing.⁷²

In order to eradicate HIV, HCV, and other STBBI as risks to public health by 2030, diagnostic testing is essential. In fact, prompt and precise STBBI diagnosis is crucial for connecting patients with the right care and treatment, averting negative consequences, and reducing the spread of infection.^{73,74} For many populations, PoCT has been demonstrated to be usually acceptable, and frequently even better than traditional testing techniques. Reaching first-time testers, increasing testing frequency among current testers, increasing the percentage of testers receiving their results, accelerating linkage to treatment and care, and lowering loss to follow-up can all be facilitated by this high acceptability and some of the unique features of PoCT (such as the availability of rapid results and flexibility in the settings in which it can

be administered). PoCT also helps reduce the danger of further transmission in outbreak situations by giving early access to test results and treatment.

Using an expressed HCV core protein as the recognition molecule, Aronoff-Spencer and colleagues developed a quantitative diagnostic for anti-HCV that is more relevant to proof-of-concept testing.⁷⁵ As the anti-HCV receptor, yeast cells expressing the HCV core protein on the surface were attached to a gold screen-printed electrode (SPE) (Figure 12.4a). Using a secondary alkaline phosphatase (ALP) tagged anti-human antibody, which catalyses a detectable reaction when exposed to its substrate utilizing cyclic

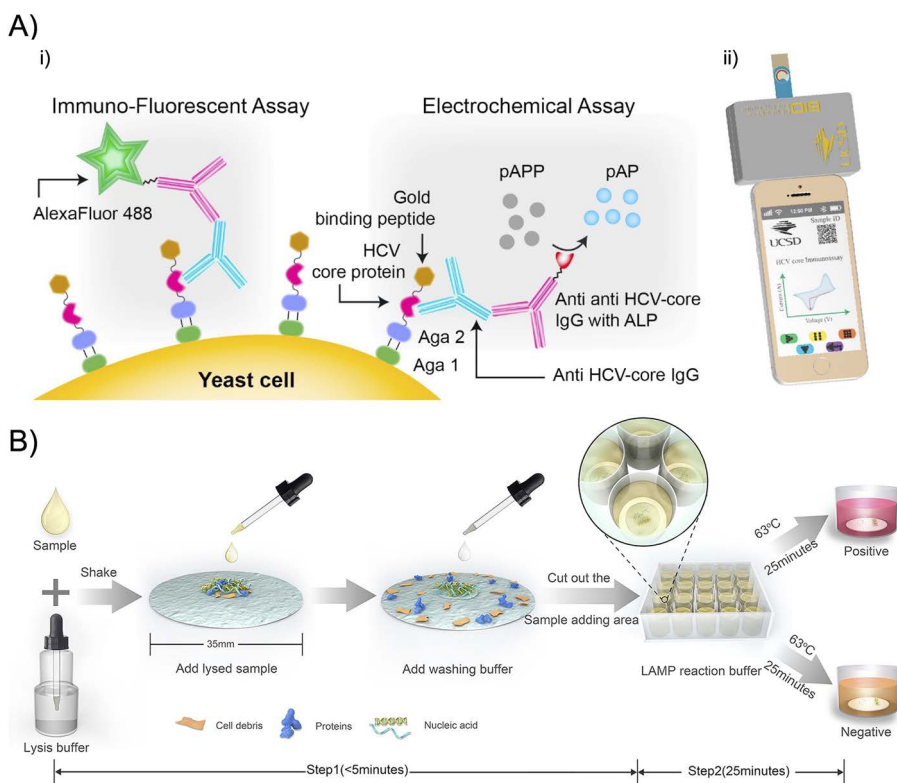


Figure 12.4 (a) Representation of a yeast biobrick chimera facilitating the detection of anti-HCV core antibodies using a PoC smartphone potentiostat platform. (i) Detection of anti-HCV core antibody *via* fluorescence and electrochemical techniques. Abbreviations: A-agglutinin (Aga) *p*-aminophenol (pAP), *p*-aminophenyl phosphate (pAPP) (ii) Depiction using a smartphone-integrated potentiostat that interfaces with a host device *via* the audio jack. Reproduced from ref. 75 with permission from Elsevier, Copyright 2016. (b) Schematic representation of the paper-based LAMP technique for the extraction, amplification, and visual interpretation of data for rotavirus A diagnosis at the point of care. Reproduced from ref. 91 with permission from Elsevier, Copyright 2018.

CV, it was possible to make the binding of the anti-HCV to the yeast protein detectable. A potential sweep technique, CV helps by finding the electrochemical signal strength (current) vs. concentration. In a buffer solution with quantified readout on a smartphone, this approach was able to reach a LOD of 2 nM and a detectable range of 4–250 nM for anti-HCV.

The GeneXpert platform (Cepheid) can perform a qualitative, *in vitro* real-time PCR Xpert CT/NG assay to identify and differentiate genomic DNA from *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.⁷⁶ The modular platform allows the assay to be performed immediately on patient specimens without manual or off-board preparation. A sample adequacy control ensures that patient samples and testing are adequate in the assay. Within 90 minutes of loading the specimen, results are accessible. The assay and platform are Conformité Européenne (CE)-marked and Food and Drug Administration (FDA)-approved for urine, endocervical, vaginal, rectal, and pharyngeal samples. The Xpert CT/NG is one of the best PoC tests for genitourinary specimens, with sensitivities over 97% and specificities over 95%.⁷⁷ The FDA has also cleared the assay for testing in pharyngeal and rectal specimens with sensitivity and specificity of 94% and 98%, respectively.⁷⁸

12.3.3 Vector-borne and Emerging Viruses

Rapidly spreading, highly lethal, and capable of causing epidemics in areas with limited resources, vector-borne and emerging viruses frequently present formidable public health concerns; here, PoC diagnostics play an essential role in their diagnosis and control. Dengue, malaria, Zika, chikungunya, West Nile, and yellow fever are just a few of the viruses that can be spread by arthropods known as vectors. Because of their high mortality rates and unpredictable behaviour, emerging viruses like Ebola, Marburg, and Nipah further hamper worldwide health initiatives. PoC diagnostics provide for efficient disease management and outbreak control by providing testing solutions that are accessible, accurate, and can be done quickly.

Mauk *et al.* used RT-LAMP to produce affordable molecular detection of Zika virus (ZIKV) without complicated instrumentation.⁷⁹ They constructed RT-LAMP primers for the Americas-dominant Zika lineage using highly conserved ZIKV genomic regions. They created a disposable microfluidic cassette for viral nucleic acid capture, concentration, isothermal amplification, and detection for PoC molecular diagnostics. Their disposable microfluidic cassette has numerous amplification reactors with silica-based nucleic acid isolation membranes at their inlets. By decoupling the sample volume from the reaction volume, this design allows great sensitivity with relatively large sample volumes. The isolation membrane captures nucleic acids that can be used as templates in RT-LAMP amplification without elution, simplifying flow management. Their microfluidic cassette can be incubated with or without battery-power. A simple, thermally insulated portable cup heated by an exothermic process was employed for chip-based isothermal amplification

without power. Raw saliva samples spiked with various ZIKV concentrations were used to test the PoC diagnostic system. The results indicated that electricity-free PoC diagnostic device could detect 5 PFU of ZIKV per saliva sample in 40 min. Without laboratory facilities, expensive equipment, or well-trained staff, this PoC diagnostic technique is similar to the benchtop assay.

Benzine and colleagues detail a molecular diagnostic approach that can reliably detect EBOV in blood samples taken at the PoC.⁸⁰ This test relies on RT-LAMP, which is a method for amplifying the EBOV glycoprotein gene. PCR tubes with a volume of 0.2 ml were used to lyophilize the final reaction formulations. A battery-operated isothermal apparatus was used to conduct the RT-LAMP reactions. The RT-LAMP assay had a limit of detection of 2.8×10^2 PFU per test for EBOV-Kikwit and 1×10^3 PFU per test for EBOV-Makona within 40 minutes, respectively. Since no nonspecific amplification was observed in blood samples spiked with closely similar viruses and other infections, it was determined that this assay was specific for the detection of EBOV. On the basis of these findings, this diagnostic test is suitable for application in the PoC setting, where it can detect EBOV in blood samples with a high degree of specificity within 40 minutes.

12.3.4 Gastrointestinal and Foodborne Viruses

Around the world, gastrointestinal and foodborne viruses still create many intestinal disorders in humans, hence generating a great health and economic burden.⁸¹ Estimates from the WHO indicate that over two billion people die each year from diarrhoea or sickness brought on by tainted food.⁸² Interactions among foodborne bacteria, hosts, food, and the environment determine the occurrence and relevance of various foodborne disorders.⁸³ Viruses including norovirus, rotavirus, hepatitis A virus (HAV), and enteric adenoviruses have been reported to cause viral foodborne diseases.⁸⁴ Common signs of foodborne disease are stomach discomfort, diarrhoea, vomiting, nausea, fever, respiratory problems, and even death in extreme situations.⁸⁵ Most of the outbreaks have been attributed to vegetables, fruits, dairy products, shellfish, ground meat, and poultry.⁸⁶ Detecting these viruses is thus crucial since they endanger public health significantly. Traditional techniques for identifying food pathogens consist mostly of plate separation, chemical analysis, and immunoassay.⁸⁷ These techniques may have drawbacks, including laborious procedures, protracted detection cycle, high expense, and high standards for a professional level of operators.⁸⁸ Thus, it is absolutely necessary to create low-cost, quick, simple, sensitive, and easy ways to identify harmful bacteria in complicated food samples. In recent years, PoC technology has become a fast evolving foodborne pathogen detection technique with benefits including easy operation, quick operation, portability, and automation.⁸⁹

The most common viral cause of acute gastroenteritis is human norovirus (HuNoV). Rapid diagnosis of HuNoVs has been significantly aided by PoC based on lateral flow immunochromatography (LIFC). Traditional LIFC, on

the other hand, has low sensitivity and a lack of quantification, which limits its usefulness. Gao *et al.* therefore created a quick and precise method combining LFIC with immunomagnetic enrichment (IM) to find genogroup II (GII) HuNoVs in faecal samples.⁹⁰ Amino-functionalized magnetic beads (MBs) and carboxylated quantum dots (QDs) were connected at a mass ratio of 4:10 before production of immunofluorescent nanomagnetic microspheres and to obtain HuNoV enrichment in IM and fluorescent signals in LFIC. QDs-MBs were then coupled with anti-HuNoV monoclonal antibody. Under ideal conditions, the limit of detection was 1.56×10^4 copies per ml and the quantitative detection range was 1.56×10^4 – 1×10^6 copies per ml. Though the prevalent HuNoV genotypes GII.2, GII.3, GII.4, and GII.17 could be found, there was no cross-reaction with other enteric viruses, including rotavirus, astrovirus, enterovirus, and sapovirus. Among 87 faecal samples, IM-LFIC and RT-qPCR produced a good degree of concordance ($\kappa = 0.799$). This implied that the approach is quick and sensitive, so it may be useful for point-of-care testing in the future.

Ye *et al.* described a very straightforward paper-based test for the PoC identification of rotavirus A, one of the most prevalent viruses responsible for paediatric gastroenteritis⁹¹ (Figure 12.4b). This paper-based test could be used to perform nucleic acid extraction in under 5 minutes, then to amplify the target sequence in 25 minutes; the outcome was apparent to the naked eye right after or quantifiable by the UV-visible absorbance. This inexpensive technique is simple to employ in a lab or at the PoC and does not call for additional equipment. Rotavirus A's detection limit was 1×10^3 copies per ml. Testing of 48 clinical stool samples yielded 100% sensitivity and specificity. Ultimately, the paper-based test met the key criteria for a PoC diagnostic tool and could be used for precision diagnosis, control, and disease prevention.

12.4 Challenges and Future Perspectives

12.4.1 Technical and Regulatory Challenges

PoC diagnostics have the potential to transform the way infectious diseases, particularly viral infections, are detected and managed. As demand for quick, on-site diagnostic solutions increases, PoC technologies provide a number of advantages, including reduced time to diagnosis, decentralization of health-care, and the ability to deliver real-time results. However, several technical and regulatory barriers need to be overcome before PoC diagnostics can reach their full potential, especially for viral detection.

Most PoCT platforms have limited capabilities for multiplex detection, which restricts their use in diagnosing co-infections or analysing biomarker panels. Moreover, these platforms often lack advanced data interpretation tools, making it difficult to extract clinically relevant insights from complex biological signals. The interpretation of results by untrained users—especially when dealing with faint or ambiguous test lines—introduces variability

and reduces diagnostic confidence.⁹² This variability can significantly affect the accuracy of diagnoses, particularly in non-laboratory settings.

PoCT devices are classified as medical devices, which means they must adhere to regulatory standards. Obtaining approval and ensuring compliance with these regulations can be a complicated and time-consuming process.⁹³ Currently, clear regulatory standards for PoCT are still lacking. PoCT is primarily guided by laboratory standards, but there is an urgent need for a regulatory framework that facilitates access to and reimbursement for these technologies.⁹⁴ The exclusion of certain tests from Essential Diagnostic Lists creates ambiguity regarding who is responsible for covering the costs, which negatively affects access to testing. Furthermore, policies for PoCT should address all stages, from test procurement and approval to the registration of results for surveillance purposes. In the post-pandemic era, funding for PoCT may be limited, requiring strategic deployment of testing strategies to ensure access for those in need. To establish whether differential diagnosis should be a public health priority, it is essential to demonstrate the value and cost-effectiveness of these testing strategies, highlighting the potential savings and reduction in future disease burden on the healthcare system and society.⁹⁵

In addition, there is a growing need for real-time data processing and automated error detection systems to improve the accuracy and reliability of results. Regulatory frameworks must also evolve rapidly to accommodate the fast-paced advancements in PoCT technology, ensuring that quality, reliability, and safety are maintained. Addressing these technical and regulatory issues is essential to enable broader and more effective integration of PoCT into global healthcare systems.⁹⁶

12.4.2 Future Trends in PoC Diagnostics

Laboratory-based diagnostic methods are well-established and continue to serve as the gold standard for virus detection. However, commercial PoCT technologies are rapidly advancing and are expected to emerge as a promising alternative for viral detection, offering convenience and accessibility outside traditional laboratory settings. The ability to detect and quantify whole viruses or virus-specific and host-derived biomarkers plays a critical role in differential diagnosis and immune monitoring, ultimately supporting more effective disease management. Thanks to recent advances in synthetic biology, signal amplification strategies, and smart materials, biosensing technologies are rapidly evolving into powerful tools for decentralized point-of-care testing. These innovations offer strong analytical performance and hold particular promise for improving viral diagnostics in low-resource settings, where access to conventional laboratory infrastructure is limited.

Advancements in materials science and nanotechnology have paved the way for the development of highly effective biosensors for pandemic control.

Among these, conjugated polymers have emerged as highly promising candidates due to their unique molecular structures, flexibility, and high sensitivity for virus detection.⁹⁷ Colourimetric biosensors, in particular, stand out for their ability to detect viruses through simple, visible colour changes, making them accessible, low-cost, and easy to use with tools like smartphones. These sensors offer excellent sensitivity and specificity, making them invaluable for both medical professionals and researchers.⁹⁸ In the future, new materials like colourimetric paper will further enhance the performance of these biosensors, opening up new possibilities for rapid and accurate virus detection.⁹⁹ On the other hand, various electrochemical biosensing techniques have been developed to achieve high detection and quantification limits for viruses, suitable for real-world applications.¹⁰⁰ Many of these biosensors are built using compact potentiostats, which are portable, battery-operated, and capable of wirelessly connecting to smartphones *via* apps that can interpret electrochemical results. Micro-nanofabrication and 3D printing techniques have played a key role in miniaturizing and enhancing the portability of these devices. For example, compact discs have been repurposed into bio-potential, electrochemical, stretchable, and flexible wearable sensors, which can communicate *via* Bluetooth® with smartphones, offering a practical solution for virus detection on the go.^{15,18} Finally, the fusion of the Internet of Things (IoT) and artificial intelligence (AI) technologies will redefine the future of PoC diagnostics. IoT connectivity will enable devices to transmit real-time data wirelessly, while AI algorithms will process and interpret this data, facilitating predictive diagnostics, personalized treatment, and remote patient monitoring.¹⁰¹ Together, IoT and AI will transform PoC devices into fully integrated, intelligent systems capable of continuous health monitoring and supporting advanced, real-time clinical decision-making.

As PoC diagnostics continue to evolve, they will become more accessible, personalized, and efficient, enhancing healthcare delivery and disease management. The potential for a patient-centred, proactive, data-driven healthcare revolution is increasingly evident, particularly through the integration of optical biosensors with emerging technologies like IoT and AI. Portable optical biosensors will play a pivotal role in shaping the future of healthcare, leading to significant advancements in diagnosis and continuous monitoring, and ushering in a new era of medical care.

12.4.3 Impact of PoC Diagnostics on Global Healthcare

The global expansion of molecular PoCT is rapidly reshaping healthcare delivery, particularly in settings with limited access to centralized laboratories. As the potential of PoCT to deliver rapid, accurate diagnostics at or near the site of patient care becomes increasingly recognized, international efforts have intensified to integrate these technologies into both high-resource and resource-constrained healthcare systems.¹⁰² Collaboration between researchers, engineers, and healthcare professionals is essential to

further enhance the selectivity, sensitivity, and specificity of these devices. It is expected that these biosensors will become indispensable tools for proactive health monitoring and on-the-spot disease diagnosis, both in clinical settings and for individual use. Continuous innovation in materials and technologies will further propel this transformation, fostering broader accessibility and enhanced patient outcomes globally.

Future PoC diagnostics will focus on making these technologies more affordable, easier to use, and compliant with necessary regulations, ensuring that they can be deployed widely and fairly. While pandemics and epidemics continue to pose significant challenges, particularly in underserved areas, ensuring the equitable distribution of PoC diagnostics in regions with limited healthcare access will be pivotal in bridging healthcare disparities. As PoC technologies evolve, they have the potential to significantly strengthen healthcare systems worldwide. By providing rapid diagnostics, improving global surveillance, and enhancing the management of viral infections both at the individual and community levels, these advancements could have a profound effect on public health worldwide.

12.5 Conclusion

This chapter has reviewed the evolving field of sensor technologies for viral detection, highlighting their working principles, clinical relevance, and possible impact on diagnostic procedures. The technological viability of portable, rapid virus testing devices and their wider consequences for clinical practice and public health have been discussed. From numerous platforms providing quick and reliable diagnosis, PoC biosensor technology has evolved. Optical PoC biosensors, employing fluorescence, colorimetric, or plasmonic detection, offer exceptional sensitivity and are optimal for real-time viral load monitoring. Moreover, portable and low-cost electrochemical PoC biosensors provide precise detection by means of measurable electrical signals produced by biological interactions. Microfluidic-based biosensors, on the other hand, combine sample processing and analysis into miniature chips, hence enabling multiplexed detection with low sample volumes. The combination of biosensors, microfluidic systems, and miniaturized electronics indicates that user-friendly, selective, and sensitive diagnostic tools are available. Especially in circumstances when time, infrastructure, and access are constrained, these technologies offer a viable alternative for conventional laboratory-based assays. In the clinical detection of many viral infections, PoC diagnostic tools are increasingly important. Rapid testing for respiratory viruses, including influenza and SARS-CoV-2, facilitates prompt isolation and treatment. Particularly in resource-limited settings, these devices enable early diagnosis and continuous monitoring for sexually transmitted and blood-borne viruses like HIV and hepatitis B/C. During outbreak scenarios, vector-borne and emerging viruses such as Zika, dengue, and chikungunya can be detected by exploiting the portability of PoC platforms.

Furthermore, foodborne and gastrointestinal viruses, like norovirus and rotavirus can be rapidly identified to prevent further spread, particularly in healthcare and community settings. Such systems, deployed in PoC surveillance, exhibit potential in providing timely information that can assist therapeutic decisions. Furthermore, the emergence of new viruses and the mutation of existing ones emphasize the need for flexibility and modularity in sensor design. Preparedness for future epidemics will require systems that can quickly change to find new viral targets. At the same time, real-time disease monitoring and customized treatment will be made possible by the combination of sensor data with AI-driven analytics, mobile health platforms, and cloud-based systems. Several elements influence the successful transformation of technological developments from laboratory to practical applications: (i) clinical validation, (ii) production scalability, (iii) user education, and (iv) data integration. Complicated and often behind the pace of innovation, the regulatory approval procedures highlight the need for cooperative systems that can accelerate assessment without compromising safety or dependability. The field is located at a crossroads of technical possibility and worldwide need. The results for PoC systems indicate the possibilities and challenges involved in building next-generation diagnostic tools. In summary, new approaches in responsive viral diagnostics will be produced by coordinated efforts among scientific, clinical, and regulatory domains thus enabling continuous development and efficient use of PoC biosensor technologies.

Acknowledgements

Fatih Inci gratefully acknowledges the support from TÜBİTAK 2232 International Fellowship for Outstanding Researchers (Project No. 118C254) and the Turkish Academy of Sciences Outstanding Young Scientists Award Program (TÜBA GEBİP). This work was also supported by the Young Scientist Awards Program (BAGEP) award from the Science Academy.

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