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CHAPTER

10

Electrochemical biosensors for detection of SARS-CoV-2

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10.1 Introduction

Pathogen detection is an essential application of electrochemical biosensors [1]. Through the integration of selective biorecognition elements with sensitive transducers, electrochemical biosensors have enabled the rapid, sensitive, and selective detection of viruses. While various studies have achieved impressive detection limits, in some cases a single virus or tens to hundreds of viral RNA molecules, the developed approaches for electrochemical detection of virus particles significantly vary in regard to device and measurement approach, such as the electrode, biorecognition element, electrochemical method utilized for transduction of target binding, and measurement format utilized (e.g., sample collection, preparation, and handling protocols). Thus, the reagents, materials, and measurement approach must be carefully considered to accurately assess the utility and time-to-results (TTR) for a given electrochemical biosensor-based assay for pathogen detection in a pandemic setting.

Since the beginning of the ongoing COVID-19 pandemic, several studies have examined the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using electrochemical biosensors. While

Sensing Tools and Techniques for COVID-19: Developments and Challenges in Analysis and Detection of Coronavirus
DOI: https://doi.org/10.1016/B978-0-323-90280-9.00011-0

polymerase chain reaction (PCR)-based assays are the gold standard for SARS-CoV-2 detection (i.e., SARS-CoV-2 antigen and antibody testing), such assays require trained analysts, PCR analyzers, various reagents, and sample preparation and handling steps. Thus, PCR-based assays typically exhibit TTR near 2-4 hours because of a combination of sample preparation and detection time (i.e., the time to prepare the sample vs. the time dedicated to binding of the target analyte to the sensor and the associated electrochemical transduction process used for detection). The clinical and public demand for rapid assays for SARS-CoV-2 antigen and antibody testing as well as mobile real-time screening platforms has led to the investigation of various biosensors for SARS-CoV-2 detection. Among these, electrochemical biosensors have received considerable attention given their synergy with low-cost functional materials for transducer fabrication, fabrication processes, and readout systems, such as miniature impedance analyzers. While all assays for pathogen detection should exhibit high selectivity and low probabilities of false negative and positive results, the demand for safe, user-friendly, and rapid biosensor-based assays for pandemic management significantly constrains the design and measurement format associated with typical biosensors. In particular, it places significant weight on the cost, reliability, simplicity, and safety of the device and measurement approach.

The development of low-cost robust electrochemical biosensors for pandemic management will require investment in research and development. An effective biosensor for use in pandemic management should exhibit a highly stable and selective biorecognition element, safe and user-friendly measurement formats (e.g., sample preparation-free formats), and mobile data acquisition and readout platforms, such as those based on smartphones and miniature analyzers. While it may be possible for experienced analysts and researchers to establish the proof of concept for pathogen detection using electrochemical biosensors in controlled research settings, such as the various molecular targets associated with SARS-CoV-2 antigen and antibody testing, there are various challenges associated with creating robust, low-cost commercial biosensors for pandemic management.

Given their potential for mass production, commercialization, and implementation in mobile, low-cost measurement formats, here, we discuss recent developments in the application of electrochemical biosensors for detection of SARS-CoV-2 (i.e., electrochemical biosensor-based assays for SARS-CoV-2 antigen and antibody testing). In addition to highlighting various electrochemical biosensors that have enabled the detection of SARS-CoV-2, we highlight advances in biosensor design and measurement formats for use in point-of-care and field-based settings. We also highlight emerging areas in the field of electrochemical biosensors for pandemic management and future challenges and directions in applications to SARS-CoV-2 rapid antigen and antibody testing.

COVID-19 disease is caused by SARS-CoV-2 infection. SARS-CoV-2 is a positive-sense single-stranded coronavirus that exhibits structural and molecular characteristics similar to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). Thus, the target species associated with SARS-CoV-2 antigen detection (testing) includes the active or inactivated virus, protein-containing viral fragments, or viral RNA. In addition, the detection of SARS-CoV-2 antibody serves as a critical target of interest for antibody testing applications.

Electrochemical biosensors can be classified as biocatalytic or biocomplexing in nature, depending on the type of biorecognition element utilized. A comprehensive review of pathogen detection using electrochemical biosensors can be found elsewhere [1]. As shown in Table 10.1, electrochemical biosensors for SARS-CoV-2 antigen and antibody detection have been primarily based on biocomplexing reactions with immobilized antibodies or single-stranded DNA probes, which are highly selective biorecognition elements. Thus, the majority of electrochemical biosensor-based assays for SARS-CoV-2 detection can be broadly classified as antibody- or DNA-based assays.

As shown in Fig. 10.1 and Table 10.1, SARS-CoV-2 (antigens) and SARS-CoV-2 antibodies have been detected through the recognition of several target species using a variety of transducers, biorecognition elements, and measurement formats [2–27]. For example, the SARS-CoV-2 spike (S) protein, nucleocapsid (N) protein, and glycoproteins have served as the target species for several antibody-based electrochemical biosensing applications to SARS-CoV-2 antigen testing. Monoclonal and polyclonal antibodies against the aforementioned protein targets have been the most commonly used biorecognition element. Monoclonal antibodies exhibit several advantages, including high reproducibility and specificity but may be vulnerable to change of the epitope, such as via S protein mutation. Thus, tracking changes associated with the genome of SARS-CoV-2 is also a critical aspect of developing rapid and selective assays for SARS-CoV-2 detection in addition to vaccine development. For example, the spike protein, a common target of electrochemical biosensor-based assays for SARS-CoV-2 detection has mutated since the onset of the COVID-19 pandemic [9]. Alternatively, polyclonal antibodies are relatively less expensive, exhibit relatively shorter production time and higher stability, and can identify multiple epitopes of a target. However, polyclonal antibodies may exhibit relatively increased batch-to-batch variability. Thus, monoclonal and polyclonal antibodies exhibit advantages and disadvantages as biorecognition elements for use in electrochemical biosensor-based SARS-CoV-2 screening technologies for rapid antigen and antibody testing.

Given their use as targets for PCR-based SARS-CoV-2 antigen testing assays, which remain the gold standard for COVID-19 diagnostics, the S

TABLE 10.1 Classification of electrochemical biosensors for detection of SARS-CoV-2 in terms of target species, sample type, working electrode, biorecognition element, electrochemical method, and limit of detection.

Target species	Sample type	Working electrode	Biorecognition element	Electrochemical method	Limit of detection	Ref.
SARS-CoV-2 RNA	Cell lysate	Au electrode	CRISPR-Cas9	SWV	N/A	[5]
SARS-CoV-2	Transport medium and human cells	Perfluorocarbon SAM-modified Au electrode	Angiotensin converting enzyme 2	EIS	37.8 dC/mL	[23]
SARS-CoV-2	Saliva	Screen printed carbon electrode	SARS-CoV-2 monoclonal antibody	DPV, CV	90 fM	[14]
SARS-CoV-2 N gene	Nasal swab; saliva	Graphene-based Au electrode	Antisense oligonucleotides	N/A	6.9 copies/μL	[2]
SARS-CoV-2	Nasal swab	Graphene-based Au/Cr electrode	SARS-CoV-2 S protein antibody	FET	2.42×10^2 copies/mL (clinical sample)	[19]
N protein, immunoglobulins against SARS-CoV-2 S protein (S1) (S1-IgM and S1-IgG); C-reactive protein (CRP)	Blood; saliva	Graphene electrode	N protein monoclonal antibody; CRP monoclonal antibody; CRP polyclonal antibody; S protein-RBD monoclonal antibody	AMP	N/A	[21]
SARS-CoV-2 S protein	Saliva	Au electrode	Anti-S protein antibody	CA	N/A	[25]
SARS-CoV-2 S protein	Saliva	Shrinky-Dink wrinkled Au electrodes	Aptamer	N/A	1 ag/mL (S1 protein)	[26]
SARS-CoV-2	Nasal swab	Carbon nanofiber-modified screen-printed carbon electrodes	Anti-N protein antibody	SWV	0.8 pg/mL	[6]

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SARS-CoV-2 N protein	Nasal swab	Poly-m-phenylenediamine (PmPD) modified Au-based thin-film electrodes	N protein imprinted PmPD	DPV	15 fM	[18]
SARS-CoV-2 S protein	Nasal swab; saliva	Cu_2O nanocubes modified screen printed carbon electrode	Anti-S protein monoclonal antibody	CV, EIS	0.04 fg/mL	[16]
SARS-CoV-2 antibody	Serum	ZnO nanowire functionalized paper-based carbon electrode	SARS-CoV-2 S protein receptor-binding domain	EIS	N/A	[12]
SARS-CoV-2 S and N proteins	Saliva	Carbon black-based screen-printed electrode	Monoclonal anti-N protein antibody; polyclonal anti-N protein antibody; Monoclonal anti-S protein antibody; polyclonal anti-S protein antibody	DPV	19 ng/mL (S protein); 8 ng/mL (N protein)	[7]
SARS-CoV-2 N protein	Serum	Screen-printed Au electrode	Anti-SARS-CoV-2 monoclonal N protein antibody	CA	50 pg/mL	[11]
SARS-CoV-2 antibody	Serum	Graphene oxide modified graphene electrode	S protein receptor-binding domain	SWV	1 ng/mL	[24]
SARS-CoV-2 antibody	Serum	Au electrode	S protein receptor-binding domain	EIS	N/A	[17]

(*continued on next page*)

TABLE 10.1 Classification of electrochemical biosensors for detection of SARS-CoV-2 in terms of target species, sample type, working electrode, biorecognition element, electrochemical method, and limit of detection—cont'd

Target species	Sample type	Working electrode	Biorecognition element	Electrochemical method	Limit of detection	Ref.
SARS-CoV-2 S protein; SARS CoV-2	Solution	Graphene electrode	Anti-S protein antibody	SWV	20 μg/mL (S protein), 5.5×10^5 PFU/mL (SARS-CoV-2)	[15]
SARS-CoV-2 S S1 antibody; SARS-CoV-2 S RBD antibody	Solution	Reduced graphene oxide-coated Au micropillar array	SARS-CoV-2 S protein RBD-His protein; SARS-CoV-2 S protein S1-His protein	EIS	2.8×10^{-15} M (spike protein), 16.9×10^{-15} M (spike protein RBD)	[3]
SARS-CoV-2 RNA	N/A	Screen printed carbon electrode	ssDNA capture probe to ORF1ab	DPV	200 copies/mL	[27]
SARS-CoV-2 glycoprotein	Nasal swab; saliva; blood	Glassy carbon electrode	Graphene oxide with sensitive chemical compounds along with Au nanostars	DPV	1.68×10^{-22} μg/mL	[8]
SARS-CoV-2 S protein	Saliva	MXene–graphene	S protein monoclonal antibody	FET	1 fg/mL	[13]
SARS-CoV-2 S and N proteins	Nasal swab	Single-walled carbon nanotube	S protein polyclonal antibody; N protein polyclonal antibody	FET	0.55 fg/mL (spike antigen), 0.016 fg/mL (nucleocapsid antigen)	[20]
MERS-CoV	N/A	AuNPs on carbon electrode	MERS-CoV antigen-antibody complex	SWV; $Fe(CN)_6^{3-/4-}$; MERS CoV-antibody complex	400 fg/mL	[10]
SARS-CoV-2 S and N genes	Nasal swab	Screen-printed carbon electrodes	S/N gene specific ssDNA probe	DPV; RCA	1 copy/μL	[4]

Abbreviations: EIS, electrochemical impedance spectroscopy; CV, cyclic voltammetry; SWV, square wave voltammetry; DPV, differential pulse voltammetry; CA, chronoamperometry; FET, field-effect transistor; RCA, rolling circle amplification; Au, gold; AMP, amperometry.

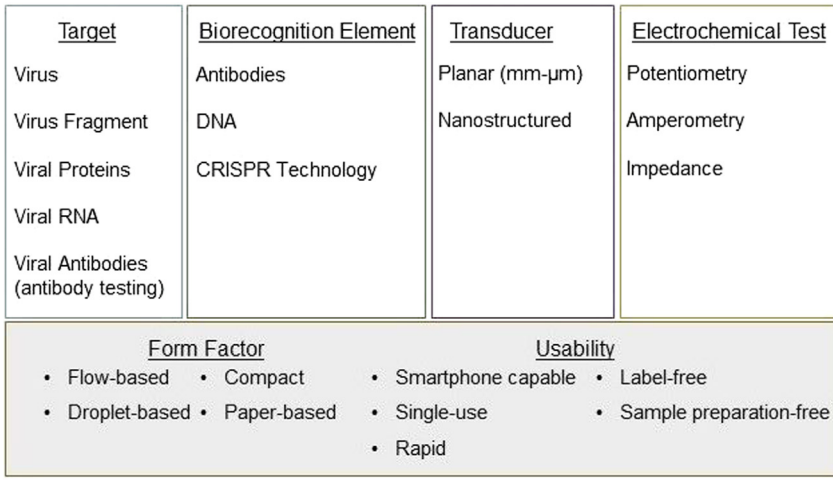

FIGURE 10.1 Components and measurement formats associated with electrochemical biosensors for SARS-CoV-2 antigen and antibody detection.

and N genes of SARS-CoV-2 have been utilized to develop selective single-stranded DNA (ssDNA) probes for electrochemical biosensor-based detection of SARS-CoV-2. A discussion of ssDNA probe design is beyond the scope of this chapter. Commercially available software now exists for probe design and optimization. In addition to antibodies and ssDNA, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology has recently received attention in the biosensing field as a novel biorecognition element, particularly for nucleic acid sensing applications. We direct the interested reader to various recently published reviews of CRISPR-based biosensors. As shown in Table 10.1, Dai et al. recently designed a CRISPR-based heterogeneous biochemical circuit, which enabled the detection of SARS-CoV-2 genome fragments via electrochemistry [5]. In that study, the target gene fragments were first specifically recognized and transformed by a pair of CRISPR/Cas9 D10A nucleases. The obtained strand structure was then translated into an arbitrary output and amplified into a concatemer via a primer exchange reaction mediated circuit wiring. The output of the heterogeneous biochemical circuit was examined by an electrochemical biosensing platform. The integrated platform was applied for SARS-CoV-2 genome analysis in human cell lysate.

As shown in Table 10.1, various working electrodes and electrode formats have been utilized for the electrochemical detection of SARS-CoV-2. Similar to recent trends in pathogen detection using electrochemical biosensors [1], the majority of electrochemical biosensor-based assays for SARS-CoV-2 antigen and antibody testing have examined planar and nano-structured and -functionalized (Au) electrodes. In particular,

graphene-functionalized electrodes have been used in several studies (see Table 10.1). One advantage of graphene is its ability to be integrated with flexible substrates, such as paper and polyimide films [21,24]. Another advantage is the availability of facile bioconjugation techniques for immobilization of biorecognition elements. Several methods exist for protein immobilization on graphene, which could be a SARS-CoV-2 antibody or antigen depending on the application. One method uses 1-pyrenebutyric acid N-hydroxysuccinimide ester or 1-pyrenebutyric acid as linker [15,19,21]. The pyrene group, which contains π-electrons, adsorbs to graphene allowing the carboxylic/ester group to react with available functional groups on the protein. Well-established EDC/NHS chemistry can also be utilized to immobilize proteins on graphene oxide or reduced graphene oxide [3,24] Li et al. also showed that a method based on MXene and APTES could achieve S protein antibody immobilization on graphene [13].

As shown in Table 10.1, several graphene-based electrochemical biosensors have achieved sensitive detection of SARS-CoV-2 using various biorecognition elements and electrochemical methods. For example, Seo et al. immobilized S protein antibody on a graphene-based field effect transistor (FET), which enabled the detection of SARS-CoV-2 viral RNA in clinical samples with a limit-of-detection (LOD) of 2.42 $\times$ 10 copies/mL [19]. In another study, Ali et al. fabricated graphene oxide-functionalized aerosol jet nano-printed 3D electrodes for SARS-CoV-2 detection [3]. The sensor-enabled SARS-CoV-2 S1 protein detection at a LOD of 2.8 fM. In addition to the S protein antibody and antigen, specific antisense oligonucleotides targeting the viral N gene were also used for detection of SARS-CoV-2 viral RNA of 6.9 copies/µL using a graphene-based electrochemical biosensor chip.

10.2 Future directions

10.2.1 Rapid and sample preparation-free assays

While Table 10.1 shows that various studies have examined the detection of SARS-CoV-2 antigens and antibodies, the target species often required sample preparation, such as extraction and amplification prior to, and sometimes during, detection. Sample preparation steps were most commonly reported in nucleic acid-based SARS-CoV-2 biosensing applications. While such approaches may provide sensitive and robust assays when performed in controlled laboratory settings by experienced analysts, they present a number of challenges for field and public use. For example, sample handling should be minimized to prevent cross-contamination. Further, the reagents associated with amplification reactions exhibit stability concerns and may impose challenging handling and storage requirements on end users. In contrast, as shown

in Table 10.2, several recently developed antibody-based electrochemical biosensor assays for SARS-CoV-2 antigen and antibody detection exhibit sample preparation-free formats. Ultimately, it is desirable to establish low-cost electrochemical biosensors for SARS-CoV-2 antigen and antibody testing that exhibit sample preparation-free measurement formats. It is desirable to avoid sample preparation steps within assays as sample preparation can increase biosafety hazards, TTR, the potential for false results, and assay cost. A list of 'rapid' electrochemical biosensor-based assays for SARS-CoV-2 antigen and antibody testing is provided in Table 10.2. Although the assays in Table 10.2 were classified as 'rapid' given the reported detection time was less than two hours (i.e., the time for target binding to be transduced to a point that the concentration can be identified or quantified), their actual TTR may be significantly increased based on sample preparation requirements, which must be well understood for each assay. In the assessment of electrochemical biosensors for SARS-CoV-2 antigen and antibody testing, we recommend that one should also consider the sample matrix (e.g., type of body fluid), the sample collection method, and the required sample volume, all of which also impact the environmental safety hazards associated with the assay. We recommend that these aspects of biosensor-based assays be described in future studies related to pathogen detection.

10.2.2 Mobile- and smartphone-based measurement platforms

In addition to creating safe, reliable, and user-friendly electrochemical biosensor-based assays for SARS-CoV-2 antigen and antibody detection, there remains a demand for mobile screening platforms. Zhao et al. recently established a smartphone-based electrochemical sensor for SARS-CoV-2 antigen testing [27]. In that study, a SARS-CoV-2 S protein RBD His protein-functionalized reduced-graphene-oxide-coated Au micropillar array electrode was interfaced with a smartphone. The smartphone-based platform enabled detection of SARS-CoV-2 antibody via electrochemical impedance spectroscopy [27].

10.2.3 Mass production of biosensors – Considerations in biosensor design and packaging

While mobile electrochemical biosensing platforms are now emerging for SARS-CoV-2 antigen and antibody testing [27], additional research is required to understand the stability of biorecognition elements used in field-based mobile biosensing applications. Creating highly stable biosensors for field, home, or clinical use is a multi-faceted challenge that will require innovative solutions in electrode and biorecognition layer design, biorecognition element engineering, packaging, and perhaps even

TABLE 10.2 Classification of electrochemical biosensors employing rapid measurement formats.

Target species	Sample collection method and type	Working electrode	Biorecognition element	Electrochemical method	Detection time	Limit of detection	Ref.
S-RBD protein	Protein solution	Cobalt -functionalized TiO2 nanotubes	Cobalt-functionalized TiO2 nanotubes	AMP	~ 30 s	0.7 nM	[22]
SARS-CoV-2 virus	Saliva spiked with Covid-19	Screen printed carbon electrode	SARS-CoV-2 monoclonal antibody	DPV, CV	10 - 30 s	90 fM	[14]
SARS-CoV-2 N-Gene	Nasal swab; saliva	Graphene-based Au electrode	Antisense oligonucleotides	N/A	< 5 m	6.9 copies/µL	[2]
SARS-CoV-2	Nasal swab	Graphene-based Au/Cr electrode	SARS-CoV-2 S protein antibody	FET	< 10 m	2.42×10^2 copies/mL (clinical sample)	[19]
N protein, IGs against SARS-CoV-2 S protein (S1) (S1-IgM and S1-IgG); C-reactive protein (CRP)	Blood; saliva	Graphene electrode	N protein monoclonal antibody; CRP monoclonal antibody; CRP polyclonal antibody; anti-S protein RBD monoclonal antibody	AMP	1 min	N/A	[21]
SARS-CoV-2 S protein	Saliva	Au coating	Anti-S protein antibody	CA	5 min	N/A	[25]
SARS-CoV-2 S protein	Nasal swab, saliva	Cu_2O nanocubes modified screen printed carbon electrode	Anti-S protein monoclonal antibody	CV, EIS	20 min	0.04 fg/mL	[16]

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SARS-CoV-2 antibody	Serum	ZnO nanowire functionalized paper-based carbon electrode	SARS-CoV-2 S protein receptor-binding domain	EIS	30 min	N/A	[12]
SARS-CoV-2 N protein	Serum	Screen-printed Au electrode	Anti-SARS-CoV-2 monoclonal N protein antibody	CA	< 1 h	50 pg/mL	[11]
S protein; SARS CoV-2	Solution	Graphene electrode	Anti-S protein antibody	SWV	45 min	20 μg/mL (S protein); 5.5×10^5 PFU/mL (SARS-CoV-2)	[15]
SARS-CoV-2 S1 antibody; SARS-CoV-2 Spike RBD antibody	Solution	Reduced graphene oxide coated Au micropillar array	SARS-CoV-2 S protein RBD-His protein; SARS-CoV-2 S protein S1-His protein	EIS	Seconds	2.8×10^{-15} M (spike protein); 16.9×10^{-15} M (spike protein RBD)	[3]
SARS-CoV-2 S protein	Saliva	MXene− graphene	S protein monoclonal antibody	FET	~ 50 ms	1 fg/mL	[13]
SARS-CoV-2 S protein; N protein	Nasal swab	Single-walled carbon nanotube	S protein polyclonal antibody, N protein polyclonal antibody	FET	2 min	0.55 fg/mL (spike antigen); 0.016 fg/mL (nucleocapsid antigen)	[20]
SARS-CoV-2 S gene; SARS-CoV-2 N gene	Nasal swab	Screen-printed carbon electrodes	S/N gene specific ssDNA probe	DPV	< 2 h	1 copy/μL	[4]

Abbreviations: EIS, electrochemical impedance spectroscopy; CV, cyclic voltammetry; Au, gold; AMP, amperometry.

machine learning and artificial intelligence. For example, while ssDNA has enabled selective detection of SARS-CoV-2 via viral RNA, it may be advantageous to consider probes based on alternative oligonucleotide chemistry, such as probes that employ locked nucleic acids or peptide nucleic acids. In addition to considering alternative biorecognition elements, it may be useful to consider materials-based biorecognition technology, such as molecularly-imprinted polymers, as opposed to molecular biorecognition elements (e.g., antibodies, ssDNA, and enzymes). Raziq et al. recently used a nucleocapsid-imprinted poly-m-phenylenediamine (PmPD) biorecognition layer on Au thin-film electrodes for detection of SARS-CoV-2 N protein with a detection limit of 15 fM [18].

10.3 Conclusions

Here, we summarize recent progress in SARS-CoV-2 antigen and antibody detection using electrochemical biosensors. A comprehensive analysis of studies reported since the beginning of the COVID-19 pandemic was provided in terms of transducer design, biorecognition element, electrochemical method, and measurement format. Critical aspects of biosensor and assay design and performance characteristics for pandemic management applications are highlighted including rapid, sample preparation-free, and mobile measurement formats.

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Non-Print Items

Abstract

Pathogen detection is an essential application of electrochemical biosensors. Through the integration of selective biorecognition elements with sensitive transducers, electrochemical biosensors have enabled the rapid, sensitive, and selective detection of viruses. While various studies have achieved impressive detection limits, in some cases a single virus or tens to hundreds of viral RNA molecules, the developed approaches for electrochemical detection of virus particles significantly vary in regard to device and measurement approach, such as the electrode, biorecognition element, electrochemical method utilized for transduction of target binding, and measurement format (e.g., sample collection, preparation, and handling protocols). Thus, the reagents, materials, and measurement approach must be carefully considered to accurately assess the utility and time-to-results (TTR) for a given electrochemical biosensor-based assay for pathogen detection in a pandemic setting.

Keywords

Biorecognition; Biosensor; COVID-19; SARS-CoV-2; Pathogen