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Transforming early microbial detection: Investigating innovative biosensors for emerging infectious diseases

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ABSTRACT

The recent global pandemic has highlighted an increase in the prevalence of communicable diseases caused by pathogens. The swift transmission of these diseases within a short timeframe presents a substantial risk to public health worldwide. The inefficiency of traditional diagnostic

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instruments, which need a time-consuming and complex process in the laboratory, is a significant obstacle to medical care. Currently, there is a high need for the advancement of early detection in order to rapidly diagnose infectious diseases and provide on-site results. This is crucial for prompt and early intervention to improve treatment outcomes. This also provides rapid testing and high-quality microbiological detection, comparable to laboratory standards, in a matter of minutes. Prompt diagnosis and subsequent treatment optimization aid in controlling the spread of infectious diseases. Currently, ongoing techniques and methods are used in the advancements of early detection through biosensors. This review examines the integration of early diagnostics with biosensors, specifically in relation to emerging and re-emerging infectious diseases, challenges, and the future perspective.

1. Introduction

In recent years, the dynamics of infectious diseases on a global scale have undergone unprecedented transformations, emphasizing the pressing need for revolutionary methodologies in early microbial detection. Emerging Infectious Diseases (EIDs), defined as illnesses caused by recently evolved infectious pathogens entering a population for the first time or diseases whose incidence, impact, or geographic range has increased, pose significant challenges to public health.[1] These diseases, influenced by various factors including environmental and conservation elements, have become intricate public health issues globally.[2] Their impact extends beyond individual and global health to the world economy, particularly affecting developing countries, and poses considerable threats to global health stability. The concept of "disease emergence' has played a pivotal role in shaping global health initiatives, notably at organizations like the World Health Organization.[3] EIDs affect both plant and human populations, contributing to the rise of antimicrobial resistance, environmental shifts, and zoonotic diseases, exemplified by lethal cases such as Covid-19, Zika virus, and Ebola virus.

The swift spread of EIDs can lead to substantial losses in individual health, national economies, and societal well-being.[4] Recognizing the paramount importance of early detection, especially in the context of EIDs, is crucial for mitigating the impact on public health, economies, and global stability. The emphasis on early detection remains central in infectious disease surveillance, with various surveillance approaches evolving, many of which leverage technological advancements.[5]

A key player in early detection strategies is the biosensor, a device that measures biological or chemical reactions by generating signals proportional to the concentration of analytes in the reaction.[6] Biosensors find applications in disease monitoring, drug discovery, and detecting pollutants, disease-causing microorganisms, and markers indicative of diseases in bodily fluids (blood, urine, saliva, sweat).[6] The evolution of biosensors is categorized into three generations (see Fig. 2) based on the integration of the bio-recognition element (bioreceptor) with the transducer. In the first generation (1st gen), biosensors measure analyte content and products of bioreceptor reactions, producing an electric response.[7] The second generation (2nd gen) incorporates additional components like auxiliary enzymes and co-reactants to enhance analytical efficiency.[7] In the third generation (3rd gen), bioreceptor molecules become an integral part of the sensing element, resulting in mediator amperometric biosensors with direct enzyme-electrode interactions.[7] The schematic representation of the biosensor is presented in Fig. 1.

This comprehensive review explores the fusion of early diagnostics with biosensors, particularly in the context of emerging and re-emerging infectious diseases, addressing challenges and offering insights into future perspectives.

2. Evaluation of biosensor technologies

2.1. Comparative analysis of leading biosensors

Anti-human chorionic gonadotropin immobilization strips with lateral-flow technology were used to create low-cost biosensors for glucose and pregnancy tests that were widely available to consumers due to advancements in electrochemical sensors and high-throughput techniques that prioritized detection limit, analysis time, and portability.[8] Innovative techniques have been produced by the application of nanomaterials like silicon, silver, and gold in biofabrification.[8,9] Real-time analysis in terms of sensitivity and specificity is one of the main benefits of these kinds of electrochemical sensors.[9] Still, cost reductions make such electrochemical

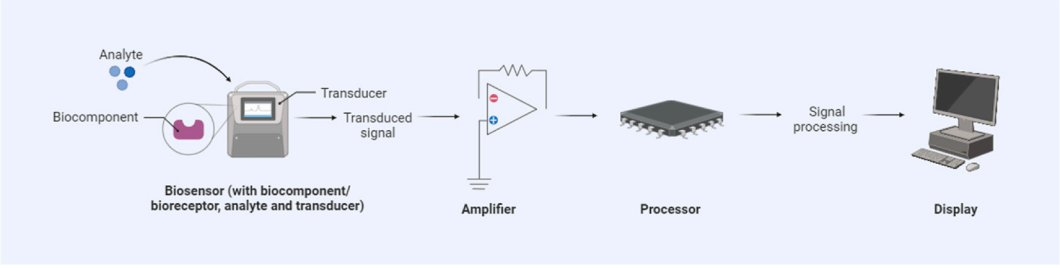

Fig. 1. Schematic representation of biosensor.[6]

sensors more accessible.[9] The drawbacks are the polymers' or other materials' limited regenerative capacity and long-term use.[9]

One of the many benefits of contact-based sensing for single analyte detection is its excellent specificity for real-time molecular measurement.[10] In order to improve specificity and sensitivity in terms of single molecule detection, Förster resonance energy transfer (FRET), fluorescent-based, bioluminescent resonance energy transfer, and surface plasmon resonance-based transducers have been presented.[10] Furthermore, 3D bioprinting using inkjet or laser direct writing yielded improved outcomes for non-contact-based sensors. However, these systems have significant limits regarding expense and customization. It is interesting to note that for some uses, the majority of these high-throughput biosensors have been paired with electrochemical sensing.[11] Using bodily fluids, some of the most renowned, sensitive, portable, and real-time amperometric electrochemical biosensors have been created for the diagnosis of illness.[11] When combined with biofabrification, electrochemical biosensors often have a low detection limit for single analyte detection specificity with real-time analysis and a reasonable cost given the device's portability.[12]

The next significant advancement in fiber-optic chemistry-based biosensing technology is optic-based biosensors. Hydrogel-based cross-linking is the most effective method for detecting single molecules, such as DNA or peptides, because of its hydrophilic nature and high loading capacity.[13] Later developments in optical biosensor technology for DNA testing led to broader applications in forensic science and healthcare.[14] Optical biosensor technology underwent a revolution with the combination of biological components, including nucleic acids, enzyme/substrate, and antibodies/antigens. Furthermore, the biosensing system can be designed to include tissue sections, animal or plant cells, and microbes.[15,16]

The main benefits of optical biosensors are their quick analysis time, signal resistance against magnetic or electrical interference, and information spectrum potential. However, because of specific instrumentation needs, the greatest disadvantage is its high cost.[17] The complexity of immobilization, particularly for biofabrication, and the need for a sterile environment are additional technological challenges that must be overcome in order to fully utilize optical biosensors.[18]

For mass-based biosensors, the process of biofabricating mechanical devices yields superior outcomes.[18] Interestingly, this technology is utilized to create ever-better biosensors using both electrochemical and optical biosensors.[19] It is now possible to create mechanical devices with nanoscale moving parts because to significant advancements in micro- and nanofabrication technology.[20] A step toward the development of useful micro- and nano-electromechanical biosensors that can be mass-produced was made possible by the capacity to create such structures using semiconductor manufacturing techniques, which bridged biophysics and bioengineering principles.[21] Materials such as silicon, quartz, and glass have been effectively tagged with gold nanoparticles or fluorescence.

Even though these biosensors are more accurate at detecting single molecules, mass manufacture at a low cost is not as practical.[22] When it comes to creating better capture agents at the nanoscale through microelectronic fabrication for high-throughput analysis, there are still many obstacles to overcome in the field of mass-based sensors.[23] The enormous application potentials of quantum dot technology and semiconductor materials are noteworthy in this regard. Nevertheless, no biosensor technology currently in use can perform simultaneous, real-time quantitative testing for huge arrays; nonetheless, the manufacture of micro- and nanoscale cantilevers may make this feasible.

2.2. *Performance metrics: sensitivity, specificity, speed*

A. Sensitivity: Biosensors are made with specific qualities and features that are dependent on their nature and mode of operation, which determines their dependability and utility.[23] The most crucial aspect of a biosensor is its sensitivity.[24] It is the lowest concentration (or amount) of analyte that can be detected, also known as the detection limit. If the targeted analyte stays close to the sensor, this feature demonstrates the sensor's ability to record any variations in its concentration. Fluctuations at tiny scales,

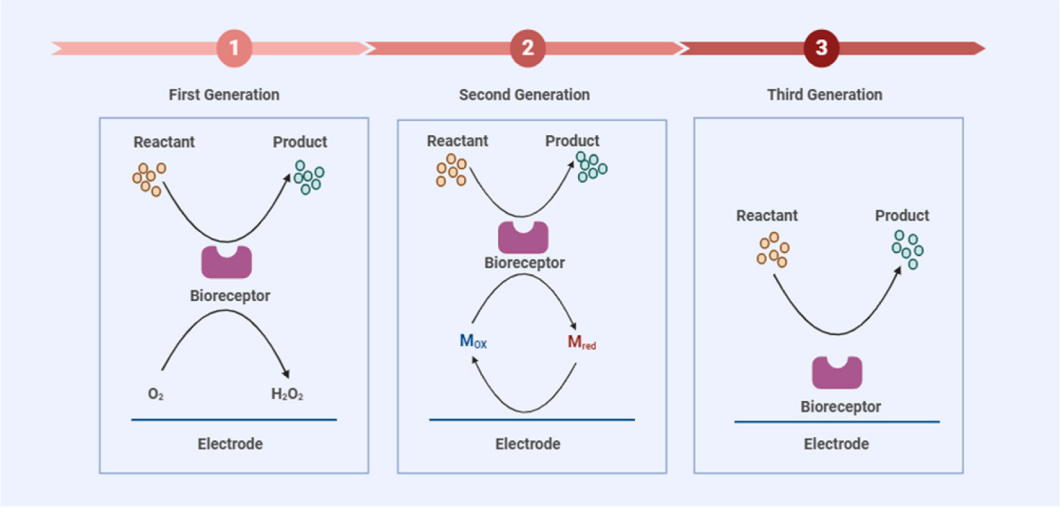

Fig. 2. Three generations of the biosensor construction (M_{OX}: Oxidized mediator; M_{Red}: Reduced mediator).[7]

including nanogram and femtogram scales, might affect very sensitive sensors. It has been reported that the sensitivity range for determining glucose is between 0.048 and 3.36 mA L mol−1 cm^2.[25,26]

B. Selectivity: This selectivity of a biosensor is predicated on its capacity to attach to or interact with a particular target analyte (molecule) when additional molecules are present in the same medium or test location. Selectivity is a crucial characteristic of biosensors used in implanted medical applications.[27] The reason for this is that the majority of bloodstream analyte possibilities have comparable characteristics, making it crucial for the bioreceptor portion of the sensor to exclusively interact with the target analyte.[28]

C. Stability: A sensor is said to be stable if its signal drifts continuously. This characteristic of the biosensor guarantees that it can tolerate noise or interference from outside sources while it is operating.[7] In this instance, noise may manifest as humidity, which has the tendency to impair the sensor signal's operational accuracy.[29] Moreover, the temperature of the human body affects the bioreceptor component of the sensor's efficacy, leading to variations in the sensor's overall output.[30] A bioreceptor's affinity for the analyte and its gradual deterioration over time are additional factors that impact stability.

D. Reproducibility: A biosensor must yield consistent output findings employing the same analyte under the same or similar settings since biosensing must be performed under delicate conditions. The transducer's capacity to display consistent findings each time the sample is sampled is a crucial feature.[31] Enhancing the repeatability and consistency of results can be ensured by regularly calibrating the biosensors in compliance with the manufacturer's instructions after usage.

E. Linearity: Linearity is the quality that demonstrates how well the measured response (for a series of measurements with various analyte concentrations) fits a straight line. This can be expressed mathematically as $y = mc$, where m is the biosensor's sensitivity, which is the output signal, and c is the analyte concentration.[32] The resolution and range of analyte concentrations under test can be linked to the biosensor's linearity. The smallest change in an analyte's concentration necessary to cause a change in the biosensor's response is known as the resolution of the biosensor. For most biosensor applications, measuring analyte concentrations over a broad working range is necessary in addition to analyte detection, hence a good resolution may be necessary.[32] Another word for linearity is linear range, which is the range of analyte concentrations for which the concentration-dependent changes in the biosensor response occur linearly.

F. Response Time: The duration required by a biosensor to read and generate a signal following its bioreceptor's interaction with a particular analyte is known as its response time. The reaction time of glucose oxidase-based sensors, for instance, ranges from 5 to 30 s.[33]

3. Diagnostic potential of biosensors

3.1. Disease identification and differentiation

Disease diagnostics heavily rely on accurately identifying and distinguishing between various diseases[34] Biosensors have emerged as powerful tools in laboratory settings for disease identification and differentiation.[35] By employing biological recognition components like enzymes, antibodies, or nucleic acids alongside transducers such as microarrays or optical sensors, biosensors can efficiently capture and identify biological molecules such as pathogens or antibodies.[36] Their high sensitivity, specificity, and real-time results make biosensors increasingly attractive for disease diagnosis, especially compared to conventional culture-based or molecular assay methods, which often involve time-consuming processes (Table 1). Biosensors offer the advantage of delivering rapid and precise results, facilitating timely intervention and appropriate patient care.[37]

One of the key strengths of biosensors lies in their ability to not only detect the presence of pathogens but also distinguish between different strains or subtypes within a single sample. This capability is particularly valuable for emerging infectious diseases, where

Table 1
Comparative analysis of biosensor types: detection principles, target analytes, advantages, and limitations.

Biosensor Type	Detection Principle	Target Analytes	Advantages	Limitations
Antibody-based	Immunoassay	Specific pathogens	High specificity and sensitivity	Need for specific antibodies for each pathogen
Nucleic acid-based	Nucleic acid amplification	Viral/bacterial DNA/RNA	High sensitivity and specificity	Requirement for PCR and specialized equipment
Protein-based	Protein-protein interaction	Disease biomarkers	Wide range of potential target analytes	Potential for false positive/negative results
Aptamer-based	Aptamer-target interaction	Pathogenic molecules	Easy modification and low cost	Limited availability of aptamers for specific pathogens
Enzyme-based	Enzyme-substrate interaction	Metabolites	Robust and reliable detection	Need for specific substrates for each enzyme
Whole-cell-based	Cellular response to pathogens	Pathogens and their toxins	Multiple target analytes and cost-effective	Risk of false positive/negative results due to interference
Nano-based	Nanomaterial's interaction	Pathogens	Enhanced sensitivity and detection at the nanoscale	Complex fabrication and potential for nonspecific binding
Optical-based	Light absorption or scattering	Disease biomarkers	Real-time and label-free detection	Limited specificity and need for appropriate detection optics
Electrochemical	Electrochemical reaction	Disease biomarkers	High sensitivity and rapid response	Potential for interference from other molecules in the sample

prompt identification and classification are crucial for effective outbreak management.[38] By identifying specific genetic markers or antigenic patterns associated with distinct strains, biosensors enable quick identification and differentiation within a sample. Additionally, biosensors can play a vital role in ongoing infectious disease surveillance, especially for conditions requiring continuous monitoring or those with a high likelihood of recurrence. Overall, biosensors offer a versatile and efficient approach to disease identification and differentiation, making them invaluable tools in the realm of public health and clinical diagnostics.[38]

Early detection plays a pivotal role in point-of-care diagnosis and the recuperation from pathogenic illnesses. Traditional methods for virus detection involve isolating and screening viruses from clinical samples, as well as utilizing polymerase chain reaction (PCR)-based assays,[39] enzyme-linked immunosorbent assays (ELISA),[40] and immunofluorescence assays. Conversely, various methods are valuable for measuring viral quantities, which include assessing viral infectivity (such as plaque assay, TCID50), quantifying viral genetic material, or protein levels (qPCR, western blotting),[41] or directly counting viral loads using flow cytometry. While these methods offer reliable accuracy, they are time-consuming, require significant labor, and may be less cost-effective due to the necessary storage and handling of chemicals. Additionally, it's worth noting that conventional diagnostic practices are impractical for on-site use because they necessitate specialized equipment and appropriate laboratory conditions. To address these challenges, biosensor-based approaches have been extensively researched for rapid detection, presenting a promising opportunity for on-site diagnosis with reduced labor and time requirements.

The progress in interdisciplinary biological research, coupled with insights from nanomaterial chemistry, has played a pivotal role in the evolution of biosensors. These devices possess physiochemical detection capabilities that allow for the identification of analytes with biological significance, marking a significant advancement in analytical technology.[42] Biosensors have the ability to translate biological responses into measurable signals, either optical or electrochemical, facilitating the detection and quantification of specific analytes. The biosensor operates by the interaction between a specific analyte and the immobilized bioreceptor, which may consist of enzymes, peptides, oligonucleotides, or DNA, resulting in the production of a detectable signal. Modifying biosensors presents a viable diagnostic method not only for established viruses but also for novel or genetically diverse virus families.

3.2. Comparative analysis with traditional diagnostic methods

Utilizing state-of-the-art technologies, biosensors provide quick and precise identification of a wide range of analytes, including pathogens and biomolecules. Contrary to conventional techniques, which frequently call for specialized laboratory equipment and time-consuming sample preparation, biosensors enable point-of-care testing, enabling on-site and real-time detection.[43] Additionally, biosensors have higher sensitivity and specificity, making it possible to precisely detect analyte concentrations even at low levels. These characteristics make biosensors especially useful in healthcare environments, like tracking chronic conditions or infectious disease outbreaks, where prompt diagnosis is essential.[43]

On the other hand, despite their widespread use and established nature, traditional diagnostic methods may have drawbacks like increased costs, longer turnaround times, and the requirement for specialized equipment and personnel with training. Furthermore, traditional techniques might call for greater sample volumes and thorough sample handling protocols, which raises the possibility of contamination and human error. All things considered, biosensors present a viable substitute to conventional diagnostic techniques, which have been vital to the healthcare industry for many years. Because of their speed, sensitivity, and accessibility, biosensors have the potential to transform diagnostic procedures and enhance patient outcomes.[43,44] Table 2 provides a summary of comparison between biosensors and traditional diagnostic methods.

Table 2
Summary of comparison between biosensors and traditional diagnostic methods.

Aspect	Biosensors	Traditional Diagnostic Methods
Principle of Operation	Detection and measurement of a target analyte (e.g., proteins, nucleic acids) using biological recognition elements	Identification and analysis of specific antigens or specific nucleic acid sequences
Sensitivity	High sensitivity (ability to detect low concentrations of analyte)	Sensitivity may vary depending on the method used
Specificity	High specificity (ability to differentiate target analyte from non-target analytes)	Specificity may vary depending on the method used
Speed	Rapid detection (real-time or near real-time)	Detection time may vary depending on the method used
Ease of Use	User-friendly operation and simple sample preparation	Requires technical expertise and lab infrastructure
Cost	Costs may vary depending on the complexity of the biosensor and the target analyte	Costs may vary depending on the method used, but can be relatively expensive
Portability	Can be designed for portable use	Requires lab-based equipment and infrastructure
Multiplexing Capability	Can detect multiple analytes simultaneously	May have limitations in detecting multiple analytes simultaneously
Sample Volume Required	Small sample volume required (e.g., microliters)	May require larger sample volumes, depending on the method used
Reliability	Can provide reliable results with low false positive/negative rates	May have variability and subjectivity in interpretation
Limitations	Limited availability for some target analytes, challenging sample matrices, potential interference from non-target substances	May have limited sensitivity or specificity for certain target analytes or sample matrices
Case Studies	Comparative analysis with case studies if available in literature	May be limited or not applicable in certain cases or diseases

3.3. Real-time monitoring and surveillance

For early epidemic detection and efficient outbreak management, real-time surveillance and monitoring of infectious illnesses is essential. Because of its capacity to detect and identify particular pathogens or genetic markers linked to infectious disorders, biosensors have become a potential tool in this area quickly and precisely. For instance, biosensors equipped with nucleic acid sequencing capabilities enable surveillance of Zika virus variants and the genetic mutations associated with changes in virulence, transmission, dynamics, and antigenic properties. Continuous monitoring of Zika virus diversity using biosensors informs vaccine development efforts and guides public health interventions to combat emerging strains of the virus. The combination of biology and technology enables biosensors to identify and measure certain chemicals or pathogens in intricate clinical samples, facilitating real-time illness progression tracking.[36]

Furthermore, biosensors offer the opportunity for continuous surveillance of infectious diseases, encompassing monitoring infections in various environmental elements such as air, water, and surfaces. By utilizing biosensors for real-time surveillance, potential epidemics can be identified early, facilitating rapid containment and intervention strategies. Biosensors serve as highly specific and sensitive diagnostic tools for detecting infectious pathogens, playing a critical role in disease management and treatment planning. Leveraging biosensors for immediate pathogen identification and differentiation enables targeted therapy and reduces unnecessary use of broad-spectrum antibiotics. Additionally, biosensors can track changes in drug resistance patterns and pathogen abundance over time, providing valuable insights into treatment efficacy.[45,46]

4. Integration of biosensors into routine laboratory workflow

In order to successfully integrate biosensors into routine laboratory practice, there is a need to employ methodological adjustments that not only ensure the accuracy of results, but also guarantee the reproducibility of experiments and diagnostic procedures. Standardization of protocols is paramount, which involves establishing clear guidelines for sample preparation, sensor application, and data interpretation, to ensure diagnostic accuracy across all laboratory analyses.

For instance, in the case of immunological biosensors employed in infectious disease diagnostics, such as Lateral Flow Immunoassays (LFIA) and Surface Plasmon Resonance (SPR) biosensors,[47] it is important to focus research and development around improving antibody immobilization methods for increased sensitivity. In addition, subsequent technologies may explore multiplexing for simultaneous detection of multiple analytes, which will greatly enhance turnaround time and optimize resource utilization.[48]

For DNA-based biosensors widely used for genomic studies and pathogen identification, the context of resource-limited settings must be considered by exploring isothermal amplification techniques such as loop-mediated isothermal amplification (LAMP) and recombinase polymerase amplification (RPA), which operate at a constant temperature.[49,49] This eliminates the need for complex thermal cyclers, thus, making DNA amplification more accessible and feasible in settings with limited resources. Such approaches can also be integrated in point-of-care applications for generating rapid results in diverse environments.[50] On the other hand, low-cost aptamer synthesis methods can be investigated in aptamer-based biosensor technologies used for cancer biomarker detection, which can improve mass production efforts and enhance applicability across diverse laboratories.[51]

While applying methodological adjustments for biosensor adoption, it is also important to note that its successful integration in routine laboratory tasks is dependent on the proficiency of laboratory personnel in biosensor operation, maintenance, and data interpretation. Hands-on technical workshops tailored to the specific features of each biosensor platform are crucial to ensure that laboratory personnel remain proficient in the use of the latest sensor platforms.[52] For instance, the plasmonic photothermal biosensors utilizing nucleotide probes for the detection of severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2) has the potential for extensive use in COVID-19 diagnosis, with laboratory personnel being trained on the technicalities of its routine diagnostic application as a means to strengthen testing capacity.[53]

Furthermore, optimizing laboratory workflows is essential, which can be implemented by incorporating biosensor-generated data into existing laboratory information management systems (LIMS).[54] This can also be supplemented by promoting the establishment of open-source biosensor platforms for easier biosensor readout. In effect, this not only enhances data accessibility but also facilitates real-time decision-making by healthcare providers, thus, expediting the diagnostic process and improving patient care.[54]

5. Challenges and future prospects

5.1. Addressing current challenges in biosensor implementation

Prompt identification of infectious disorders and quick commencement of suitable therapy are crucial factors that support both public health and the best possible clinical results. Traditional in-vitro diagnostics for infectious disorders take a long time and call for large, centralized facilities, skilled technicians, and heavy machinery. Modern advances in biosensor technology may enable point-of-care diagnostics to meet or exceed accepted benchmarks for cost, speed, and accuracy.[55] Biosensors provide the potential for an affordable, sensitive, and user-friendly technological platform for infectious diseases that may quickly identify pathogens and forecast successful treatment.[56]

Despite the necessity for clinical applications, only a few noteworthy biosensors—like the glucose sensor and lateral flow assays such as the home pregnancy test[57] have been successfully translated from research labs to clinical settings.[55] Overcoming these challenges is crucial for realizing the full impact of biosensors in revolutionizing early detection in laboratories. In this section, we will discuss some of the current challenges and propose potential solutions and future prospects.

5.2. Sample preparation

Pathogen-specific and host immunity biomarker detection has become extremely sensitive due to developments in biosensor technology and signal amplification. Unfortunately, sample preparation has been more and more acknowledged as the main obstacle to transitioning biosensors from the lab to the clinic.[82] A biosensor's adaptability and utility are significantly diminished if sample preparation is done entirely manually.[83] Target analyte enrichment, matrix inhibitor removal, and sample volume reduction are steps in the preparation of samples. The target analyte concentration, sample volume, and biological sample type all influence the sample preparation technique. The first step in sample preparation involves specimen collection, which can be done via a lumbar puncture to obtain cerebrospinal fluid, a buccal swab to gather somatic cells, a blood draw for assessing serum analytes, or a collection container to gather samples of stool, urine, or sputum.[55] Samples are put onto the sensing device for processing and analysis after collection.

On the other hand, loading a specimen can be rather simple for aqueous samples, such as spinal fluid, blood, urine, and saliva,[58] for viscous or solid materials, additional procedures like homogenization and digestion are required (i.e., stool and sputum.[59] Microfluidics has unique properties that make it perfect for point-of-care sample preparation. These characteristics include small feature sizes (ranging from nanometers to hundreds of micrometers), laminar fluid flow, fast thermal relaxation, length scale matching with the electric double layer, low fluid volume handling, short assay times, and low power consumption.[60] This review covers several microfluidics-based sample preparation platforms that are based on the two main processes of sample processing: concentration, and separation.

Numerous diagnostic tests rely on a preliminary phase of separation. Blood samples that are frequently fractionated into plasma, buffy coat, which is rich in white blood cells, and red blood cells are especially prone to separation.[61] Centrifugation and filtration are the standard methods used in clinical laboratories to separate blood.[62] Although centrifugation is quite effective, it requires specialized equipment that can be difficult to integrate with other sample preparation processes.[63] Despite being less cost-effective than centrifugation, filtering can have problems including hemolysis at high pressure and membrane clogging.[64] In order to make integration with sophisticated biosensors easier, microfluidic-based separation options are being actively researched.[65]

Both separation and concentration are typically required for biosensor detection since genuine clinical samples are typically milliliter-scale and the target analyte is present in relatively low quantities.[7] Bead-based analyte capture in conjunction with microfluidic devices has been shown to efficiently concentrate samples because of the beads' quick diffusion and high surface-to-volume ratio in solution, which give target analytes or pathogens additional binding sites.[66] Nonetheless, the imposed flow condition typically places a limit on bead manipulation.[55] Other microfluidic devices manipulate samples using electrokinetic. The study of how suspended particles move and behave when subjected to electric fields is known as electrokinetic.[67] As a short-range particle force that can act directly on a particle, DEP is one of the most promising methods for concentrating and separating pathogens and cells among other electrokinetic techniques.[68] A polarizable particle experiences the induction of a dipole when exposed to an electric field.

Depending on the conductivity and permittivity of the particles, the surrounding medium, and the applied electrical frequency, the particles will experience a net force toward (positive DEP force) or away from (negative DEP force) the electrode surface if the electric field is non-uniform. Effective separation of various-sized particles or cells is made possible by the DEP force's proportionality to particle volume. Positive DEP trapping is not successful in biological fluids with high conductivity ($\geq$1 S/m), which is the main challenge.[69] In order to get over this restriction, Park et al. paired positive DEP traps with a negative DEP-based separation channel, which allows *E. coli* to be continually separated and trapped from entire blood samples or human cerebrospinal fluid.[70]

Microfluidic systems, on the other hand, provide throughput processing, enhance transport for controlling the flow conditions, increase the mixing rate of different reagents, reduce sample and reagents volume (down to nanoliter), increase the sensitivity of detection, and utilize the same platform for both sample preparation and detection.[65] Given these benefits, combining microfluidic and biosensor technologies unlocks new possibilities for biosensing applications in the future, such as portability, disposability, real-time detection, unprecedented accuracy, and simultaneous analysis of multiple analytes in a single device. It also allows chemical and biological components to be combined into a single platform.[71]

5.3. Sensitivity and specificity

Achieving high sensitivity and specificity is vital for accurate detection of infectious agents. Many biosensors face challenges in distinguishing between closely related pathogens or exhibiting false positives/negatives.[72] Attaining maximum specificity in biosensor design is a challenging endeavor. False-positive results might arise from cross-reactivity, in which the biosensor identifies unintentional analytes that share similar features.[73] Continuous refinement of bio-recognition elements and incorporation of advanced nanomaterials can enhance sensitivity and specificity.[74] An investigation by Rakesh et al. explores the complementary integration of nanotechnology and biotechnology, leading to sophisticated biosensing techniques for health care diagnosis.[75]

In order to detect a wide range of biological events, including pathogenic and poisonous agents, it is necessary to understand the production and classification of various nanomaterials, as well as their unique chemical and structural characteristics.[76] The discourse extends to a critical analysis of biosensors, categorizing them based on bio-recognition elements and signal transduction mechanisms integral to medical applications.[74]

Additionally, it addresses the dynamic and evolving landscape of biosensing technology while scrutinizing the challenges encountered in the practical application of nanomaterials in medical biosensing frameworks.[77] Also, ongoing research in molecular biology can contribute to the identification of unique biomarkers for precise pathogen detection.[78]

5.4. Multiplexing

Detecting multiple pathogens simultaneously (multiplexing) is essential for a comprehensive diagnostic approach. Existing biosensors often struggle with the simultaneous detection of various biomarkers.[79] Integration of advanced microfluidics and improved sensor arrays can enable multiplexing capabilities. Developing innovative signal amplification strategies and utilizing miniaturized, high-throughput platforms can enhance the ability to detect multiple targets concurrently.[80]

Quantum dots are often employed photoluminescent nanoparticles and are frequently selected for various multiplex systems. Nonetheless, with their distinct optical characteristics, nanoparticles including gold, silver, and rare earth metals represent a new development in the multiplexing industry.[81] Hence, the concept of multiplexing, where multiple analytes can be detected in a single sample, can be tackled using several types of nanomaterial-based biosensors.

5.5. Cost and accessibility

High development and production costs can limit the widespread adoption of biosensors, especially in resource-limited settings.[56] It is generally an uphill struggle to manufacture biosensors at a low cost without sacrificing quality or function. In addition, scalability presents financial and logistical difficulties, especially in large-scale manufacture and deployment.[82] Streamlining manufacturing processes, utilizing cost-effective materials, and promoting open-source designs can contribute to reducing overall costs.

Collaborations between research institutions, industry partners, and regulatory bodies can facilitate the development of affordable and accessible biosensor technologies.[83] To simplify biosensor manufacture and lower costs while increasing accessibility, researchers are investigating novel fabrication procedures. The integration of biosensors with existing healthcare systems and infrastructure and sensor biofouling.

This includes resolving incompatibilities, standardizing data formats, and enabling smooth connections between data management platforms and biosensors. The objective is to guarantee biosensor-generated data interoperability and effective use for well-informed clinical decision-making. Another problem is the biofouling of sensors. The buildup of organic material on the sensor surface is referred to as “biofouling,’ and it can cause erroneous readings and decreased sensor performance.[84] Researchers are actively investigating novel surface coatings and anti-fouling strategies to mitigate the effects of biofouling and maintain the integrity of biosensor measurements.

6. Specific infectious diseases and plausible biosensor approaches

Biosensors offer important insights into the dynamics of disease and the effectiveness of treatment by being able to identify and measure particular biomarkers linked to the course of a disease or its response to therapy.[85] A crucial component of biosensor application is their integration into current laboratory operations. This entails tackling issues including assay performance validation, biosensor technology standardization, and compatibility with current diagnostic systems.[86]

Dengue fever, a viral illness transmitted by mosquitoes, is triggered by the dengue virus (DENV), which comprises a single-stranded positive-sense RNA. Common symptoms of dengue infection include high fever, rash, vomiting, and nausea, typically manifesting around 3–12 days post-infection. Clinically, there are four distinct serotypes of DENV.[1-4] Although DENV infection commonly results in mild, symptom-free illness, severe cases can progress to shock syndrome and even death. While no specific treatment exists for DENV infection, prompt diagnosis and appropriate medical care significantly lower the risk and mortality rate to less than 1 % in severe dengue cases.[87]

Traditional techniques for detecting DENV in biological samples include virus isolation, qPCR, and ELISA tests utilizing DENV-specific antibodies. While these methods produce reliable results, they come with logistical challenges and involve various steps for sample preparation, making rapid on-site testing impractical. Recent advancements have led to the development of biosensors for swift DENV detection. One such biosensor, targeting DENV genetic material as the analyte, utilizes palladium and platinum with zinc nanoparticles as the matrix, offering enhanced catalytic efficiency and a larger surface area.[87]

A sequence complementary to a conserved region in the genome of all four DENV serotypes was employed as a receptor for virus detection. Additionally, an important consideration in biosensor development involves targeting the nonstructural protein 1 (NS1) of DENV. Detecting NS1 is advantageous as it enables early infection detection in both mosquitoes and hosts. However, virus detection from the vector entails numerous time-consuming and labor-intensive steps, necessitating specialized expertise and costly equipment. To address this issue, it is fitting to create a biosensor for detecting DENV NS1. NS1 is a thoroughly researched viral protein found in patient sera, making it an ideal biomarker for biosensor development. As a proof of concept for surveillance, an immunosensor was devised to quantify the NS1 protein levels in adult mosquito homogenates.[88] Monoclonal antibodies targeting NS1 were attached to single-wall carbon nanotubes and then fixed onto a gold microelectrode. The presence of NS1 protein in the sample triggered an electrochemical signal through antibody interaction, confirming detection. This biosensor design offers advantages in terms of cost-effectiveness and adaptability for detecting analogous analytes. Additionally, affinity peptides have been crafted and selected for NS1 detection in clinical samples.[89]

Zika virus (ZIKV), a member of the Flavivirus family, is primarily transmitted by mosquitoes. It was first observed in monkeys and later detected in humans in 1952. ZIKV infections have predominantly occurred in Africa, Asia, and the Americas in recent years. While the infection typically results in mild illness, it can lead to severe complications if not adequately treated, often requiring hospitalization. Prolonged ZIKV infection, particularly during pregnancy, is linked to serious birth defects such as microcephaly and abnormal brain development in the fetus. Additionally, ZIKV infection has been associated with Guillain-Barre syndrome in adults, a condition

characterized by the immune system attacking and damaging nerve cells.[90]

Many individuals infected with ZIKV exhibit either no symptoms or only mild ones. Traditionally, the presence of ZIKV in blood or urine is detected by testing for viral RNA or IgM antibodies, both of which are known to be time-consuming and economically impractical. Currently, there is no specific treatment for ZIKV infection. Hence, it is crucial to emphasize the demand for swift and exceptionally sensitive on-site detection of ZIKV through advanced biosensing technologies. Various biosensing platforms have been developed to focus on ZIKV proteins as analytes. By targeting nonstructural protein 1 (NS1) and domain III of the envelope protein (EDIII), a biosensor has been showcased to detect ZIKV antigens simultaneously.[91]

A chimeric recombinant protein, comprising both NS1 and EDIII, served as the receptor to prevent cross-reactivity with DENV. Antibodies were immobilized on the conductive carbon surface to aid in antigen detection and subsequently quantify the viral load. Consistent and systematic monitoring of ZIKV prevalence in mosquitoes within affected regions is a crucial approach to mitigate the risk of infection spread. The distinctive electrostatic surface at the *C*-terminal of ZIKV NS1 allows for its differentiation from other flaviviruses.[92] This distinctive trait has enabled the production of antibodies tailored specifically to ZIKV NS1, thereby preventing false positives resulting from cross-reactivity. A graphene-based biosensor was fabricated, with this *anti*-NS1 antibody functionalized on the surface to exclusively detect ZIKV. Recombinant ZIKV NS1 served as the target to elicit a measurable response, and this configuration effectively demonstrated rapid and precise virus detection. When assessed against other flaviviruses, the biosensor did not yield the anticipated signal. Biosensing platforms of this nature can prove highly valuable for conducting controlled surveillance of virus circulation in vectors, akin to approaches used for viruses such as Japanese encephalitis.[90]

The CRISPR/Cas9 system was initially identified as a bacterial defense mechanism aimed at detecting and degrading foreign genetic material. Subsequently, an optical geno-biosensor was created utilizing the CRISPR/Cas9 system to selectively target ZIKV RNA.[90,93] As a paper-based cell-free system, employing this biosensor for real-time on-site diagnostics offers considerable advantages. The platform exhibits exceptional specificity, as the precise hybridization between the biosensor recognition material and viral RNA, facilitated by the CRISPR/Cas9 system, enables the detection of nucleotide sequence mismatches from other viruses, as evidenced in trials involving DENV RNA. The biosensor's mechanism relies on the hybridization of ZIKV RNA, which subsequently regulates the synthesis of chromogenic substances, producing a measurable signal. Evaluation with DENV RNA revealed insufficient RNA amplification to yield a satisfactory signal, underscoring the biosensor's specificity for ZIKV RNA detection.[90]

Hybridization methods were utilized to create a potent biosensor for detecting viruses. A molecularly imprinted polymer (MIP) electrochemiluminescence biosensor was created for specific detection by utilizing an aptamer sensitive to the HIV gene.[94] Europium sulfide nanocrystals exhibit significant chemiluminescent properties. The gene-specific aptamer was utilized as a template for the identification of HIV genes. This technique showed the capability to focus on HIV genetic material as an analyte, which can be quickly detected using comparable biosensing technologies. A biosensor efficiently detected the protein from the sample by using a structural epitope or immunodominant area of the gp41 as an analyte.[95] The gp41 epitope was imprinted on the quartz crystal microbalance chip, demonstrating a strong affinity for binding the protein with specificity. A label-free optical sensing technology utilizing nanostructured photonic crystals has enabled the capture of intact viral particles, allowing for the detection and quantification of viruses in biological samples.[96] The virus adsorption and binding on the biosensor surface caused a change in the resonant peak wavelength value, which was then analyzed to determine the virus concentration.

A nano sensor was created with a DNA probe attached to the biosensor to specifically bind to the genetic material of the influenza virus.[97] The hybridization of the DNA probe and viral DNA altered the conductivity of the electrode surface, which was directly proportional to the virus concentration in the sample. A fluorescent biosensor was created to identify recombinant hemagglutinin protein of the H5N1 influenza virus in human serum.[98]

7. Anticipated developments and future directions

As a result of their revolutionary effects on a global scale, biosensors have been heralded as game-changers in the research sciences and healthcare. Significant breakthroughs have been made as a result of their incorporation into a variety of disciplines, increasing the effectiveness, precision, and accessibility of diagnostic procedures globally. The future of biosensors for early detection holds promising advancements. The incorporation of artificial intelligence for real-time data processing, the advent of wearable and portable biosensors for ongoing surveillance, and the extension of biosensor applications beyond infectious diseases to chronic ailments are among the anticipated advancements.[99] Additionally, ongoing advancements in nanotechnology, materials science, and bioengineering will likely contribute to the development of more robust and versatile biosensor platforms.[100]

The biosensors, along with the Internet of Things, Artificial Intelligence, and 5G make this sector more confident, sensitive, and customized.[101] Recently, there has been an increase in the integration of artificial intelligence (AI) with functional electronics, giving rise to a new class of intelligent systems that may use machine learning algorithms to detect, analyze, and make decisions.[102]

The 5G network's fast transmission rate will enable the gathering rate of sensor data to fulfill the demands of big data analysis and advanced artificial intelligence.[101] Intelligent systems that mix several sensors and AI technologies can analyze collected data sets more thoroughly and complexly than those that use conventional techniques. By adopting the right algorithms, adjusting their parameters, and merging different kinds of data from multiple sensors, prediction accuracy can be improved.

Biosensors have been developed and implemented into mobile apps from the laboratory. Health data collection and analysis in decentralized settings is expanding due to advancements in mobile biosensors that integrate advances in materials science and instrumentation.[103] For instance, biochemical markers can be measured using microfluidic-based sensors, while vital signs can be measured using semiconductor-based sensors.[103] Biosensor chip technology could be inserted into the body to diagnose complex blood DNA mutations before any disease signs in the early stages of development.[104] The development of this technology will provide rapid

growth, including patient satisfaction, in the healthcare industry. Fig. 3 shows the evolution of wearable sensors and virtual reality technologies aiming at digital twins.

In the field of biomedical diagnostics, the advent of biosensor technology which combines biological elements and physicochemical detectors represents a revolutionary development.[56] These advanced instruments are designed to translate biological interactions into measurable electrical signals, enabling the quick, sensitive, and targeted identification of a wide range of analytes. Biosensors enable ceaseless monitoring of persistent conditions like diabetes, ensuring proactive management and averting complications.[18] Biosensors with early warning capabilities discern subtle shifts in biomarkers, allowing swift intervention in conditions like heart disease and renal disorders.[56]

Again, Biosensors guarantee accurate changes for gene therapy applications, expanding to the complex field of gene editing. Gene therapies, powered by biosensors, have the potential to end hereditary diseases that were previously unbeatable, ushering in a revolutionary period in medical research.[105]

Biosensor approaches will investigate the expanding range of alternatives in the future to create precision medications, equipment, and diagnostics. Technological developments, interdisciplinary cooperation, and ongoing research are needed to address these particular constraints. By overcoming these barriers, biosensors will reach their full potential and be able to be seamlessly integrated into a variety of domains, leading to revolutionary improvements in environmental monitoring, healthcare, and other fields.

8. Conclusions

The need for novel approaches in early microbiological detection and disease surveillance has become more pressing due to the rise of Emerging Infectious Diseases (EIDs) in recent years. In this endeavor, biosensors have proven to be invaluable tools, providing quick, sensitive, and specific detection of disease biomarkers and infectious pathogens. Biosensors have demonstrated their versatility and efficacy in the detection of infectious diseases, from identifying viral pathogens such as Dengue fever and the Zika virus to developing novel biosensing platforms for on-site diagnostics. However, obstacles including sample preparation complexity, budgetary constraints, and the requirement for standardization stand in the way of their successful integration into standard laboratory workflows. Addressing these challenges requires collaborative efforts among researchers, industry partners, and regulatory bodies to streamline manufacturing processes, promote cost-effective fabrication methods, and ensure data interoperability.

Notwithstanding these difficulties, the potential of biosensors to transform infectious disease diagnosis and management is undeniable. Through the utilization of technological innovations and interdisciplinary teamwork, biosensors have the potential to significantly reduce the adverse effects of infectious diseases on public health, economies, and worldwide stability. Biosensors have the potential to revolutionize disease surveillance, enable early detection, and guide appropriate therapeutic interventions, ultimately contributing to a healthier and more resilient world. To fully harness their capacity in addressing infectious diseases and protecting global health, ongoing research, innovation, and investment are imperative for advancing biosensor technologies.

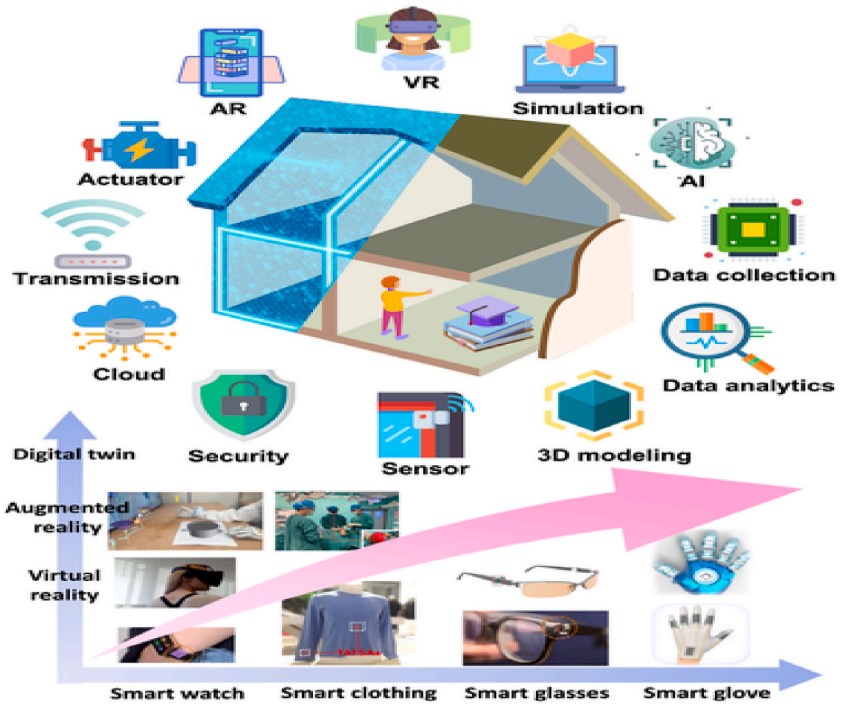

Fig. 3. The evolution of wearable sensor and virtual reality technologies aiming for digital twin 104.

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Declaration of competing interest

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