SIN-CHN SCIENTIFIC PRESS PTE.LTD.

Molecular & Cellular Biomechanics 2025, 22(3), 911.
https://doi.org/10.62617/mcb911

Article

Recent progress on the application of biosensors in biomechanics for the early detection of infectious diseases

Hui Zhang[1,2], Bingqing Xu[2], Ngit Shin Lai[1,*]

[1] Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia (USM), USM 11800, Malaysia
[2] College of Medicine, Huanghuai University, Zhumadian 463000, China
*** Corresponding author:** Ngit Shin Lai, laingitshin@usm.my

CITATION

Zhang H, Xu B, Lai NS. Recent progress on the application of biosensors in biomechanics for the early detection of infectious diseases. Molecular & Cellular Biomechanics. 2025; 22(3): 911. https://doi.org/10.62617/mcb911

ARTICLE INFO

Received: 26 November 2024
Accepted: 23 January 2025
Available online: 27 February 2025

COPYRIGHT

Copyright © 2025 by author(s). *Molecular & Cellular Biomechanics* is published by Sin-Chn Scientific Press Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license. https://creativecommons.org/licenses/by/4.0/

Abstract: Infectious diseases continue to pose a significant threat to global and public health, particularly in regions with limited access to well-equipped medical facilities. This project focuses on the application of biosensors in biomechanics for the early detection of infectious diseases. Biosensors are analytical devices used to detect various biomolecules, such as bacteria, viruses, and protein biomarkers. To enhance their effectiveness in integrated diagnostics, it is crucial to develop biosensors that are both rapid and highly sensitive. This research explores the potential of biosensors in biomechanics for the early identification of infectious diseases, with a focus on their design, functional mechanisms, and overall efficacy. Biosensors can be integrated with biomechanical principles to enhance their detection performance and range of use. For example, piezoelectric crystal biosensors can convert mechanical vibrations or pressure changes into electrical signals, enabling the detection of biomolecules when they interact with the sensor surface. Additionally, biosensors can be used to detect the mechanical properties of cells, such as cell stiffness and adhesion forces, which are significant for studying cell states and disease progression. The results suggest that biosensors present a viable option for early diagnosis, offering reliable, rapid, and cost-efficient alternatives to traditional diagnostic methods. The development of quick, highly sensitive biosensors could bridge the gap in early detection of infectious diseases, providing timely interventions that could reduce the spread and impact of such diseases. Furthermore, the integration of biosensors with biomechanical principles can lead to innovative diagnostic tools that not only detect the presence of pathogens but also provide insights into the mechanical changes associated with disease progression.

Keywords: biosensor; infectious diseases; biomechanics; classification of biosensors; medical diagnostics; recent applications; intelligence

1. Introduction

Infectious diseases are caused by pathogenic microorganisms, including bacteria, viruses, and parasites or fungi. Many of these diseases are communicable, meaning they can be transmitted from one host to another. Common infectious diseases include COVID-19, malaria, influenza, and chickenpox. According to the World Health Organization (WHO), the recent outbreak of the coronavirus in 2019 (COVID-19) has resulted in the deaths of over 600,000 people, with nearly 487 million confirmed positive cases [1]. This pandemic has had profound and unprecedented effects on social, health, and economic levels.

The control and management of infectious diseases encounter significant hurdles, such as the misuse of antibiotics, the proliferation of multidrug-resistant pathogens, the emergence of new infectious agents, continual viral mutations, and the rapid

disease transmission facilitated by globalization and overpopulation. This underscores the urgent need to develop rapid, accurate, sensitive, and cost-effective diagnostic techniques and tools to screen infected hosts, thereby interrupting the infection chain and enabling timely and appropriate treatment for those affected.

Currently, diagnostic techniques used to test for bacterial, mycotic, viral, fungal, and parasitic pathogens are based on a variety of laboratory methods, including microbial culture, immunoassays, microscopy, and nucleic acid amplification techniques [2]. Although these in vitro diagnostic methods are widely utilized today, they come with acknowledged limitations. Microscopy, for instance, often lacks sensitivity in many clinical contexts, while microbial cultures are time-consuming, leading to significant delays in diagnosis [3]. Immunoassays, such as Enzyme Linked Immunosorbent Assay (ELISA) offer high sensitivity but can be labor-intensive. Molecular biological tools, such as nucleic acid amplification tests like Polymerase Chain Reaction (PCR) require complicated sample preparation and carry a risk of false positives. Standard diagnostic procedures for common infectious diseases typically involve the collection and transportation of biological samples from the point of care to a centralized laboratory, where sample processing is completed. This process usually takes anywhere from a few hours to several days to yield results [4]. This inherent inefficiency complicates the provision of evidence-based care and often leads to the inappropriate use of antibiotics. The drawbacks of standard diagnostic methods are even more pronounced in low-resource and non-traditional medical settings.

Given these challenges, there is a pressing need to introduce more efficient methods and tools for the prevention and control of infectious diseases. Recently, there has been increasing interest in the use of biosensors in this field. Biosensors are interdisciplinary devices that integrate bioactive materials (such as enzymes, proteins, (Deoxyribonucleic acid) DNA, antibodies, antigens, and biological membranes) with physicochemical transducers [5]. These advanced detection and monitoring tools are essential for the development of biotechnology and for the rapid, trace-level analysis of substances at the molecular level. Biosensor technology has broad applications, ranging from clinical diagnostics, industrial control, and food safety to pharmaceutical analysis (including the research and development of biological drugs), environmental protection, and various biotechnology and biochip research fields [6].

As analytical devices, biosensors use transducers to convert the molecular recognition of a target analyte into a measurable signal. This capability provides a sensitive, cost-effective, and user-friendly platform for rapidly identifying pathogens and predicting effective treatments for infectious diseases. The advantages of biosensors include their short processing times, small sample volume requirements, and the potential for reuse [7].

The nanomaterial-based biosensor detection method completes the sensitive and rapid determination of pathogenic bacteria by introducing nanomaterials into the biosensor. Among them, biosensors are a kind of biological instruments that use physical and chemical detection equipment to determine various biological components, and nanomaterials have the advantages of small size, large surface-to-body ratio, surface activation, good signal conduction and conductivity, etc., and can be modified by high-density recognition molecules, which can be used as both recognition elements and signal elements, so that the detection performance of

biosensors can be effectively improved [8]. Compared with traditional methods, nano-biosensor-based detection methods have the advantages of sensitive and time-saving, real-time detection, low operation requirements, low material consumption, and low limit of detection (LOD). Recent advancements in nanotechnology have further enhanced the ability of biosensors to conduct complex molecular tests for a variety of infectious diseases. Simultaneously, significant progress has been made in understanding pathogen genomics and proteomics, as well as the interactions between pathogens and their hosts [9].

2. Principle and application

2.1. Application of biomechanical principle

Biosensors often incorporate biomechanical principles in their design and application to enhance their detection performance and range of use. In certain biosensors, biomechanical principles are used to design force-sensitive elements, such as piezoelectric crystal biosensors. Piezoelectric crystals can convert mechanical vibrations or pressure changes into electrical signals. When biomolecules interact with the sensor surface, they cause changes in the vibration frequency or amplitude of the piezoelectric crystal, thereby enabling the detection of biomolecules.

Biosensors can be used to detect the mechanical properties of cells, such as cell stiffness and adhesion forces. By applying mechanical forces or measuring the cell's response to mechanical forces, mechanical information about the cells can be obtained. This is significant for studying cell states and disease progression [10].

In wearable biomechanical sensors, biomechanical principles are used to monitor human movement and mechanical signals, such as detecting changes in skin strain and muscle contraction forces to analyze human movement and health conditions.

2.2. The principle of biosensors detecting biological signals

Biosensors generally consist of a similar structure that includes one or more bioactive materials (such as biofilms) coupled with physical or chemical transducers (sensors). These transducers are responsible for converting the signals generated by bioactive expressions into electrical signals [11]. The integration of these elements is enhanced by the latest advances in microelectronics and automated measurement technologies, leading to the development of various biosensor analyzers and devices that function as a unified system. The analyte diffuses into the bioactive substance, where molecular recognition triggers specific biological reactions. The physical or chemical transducer then converts the resulting data into an electrical signal that can be measured. This signal is further amplified and processed by a secondary device, enabling the determination of the target substance's concentration. A comprehensive schematic of the biosensor components (**Figure 1**) [12] is illustrated.

Illustrates the key components of a typical biosensor, including the bioreceptor, transducer, and signal processor, highlighting their roles in detecting and quantifying analytes.

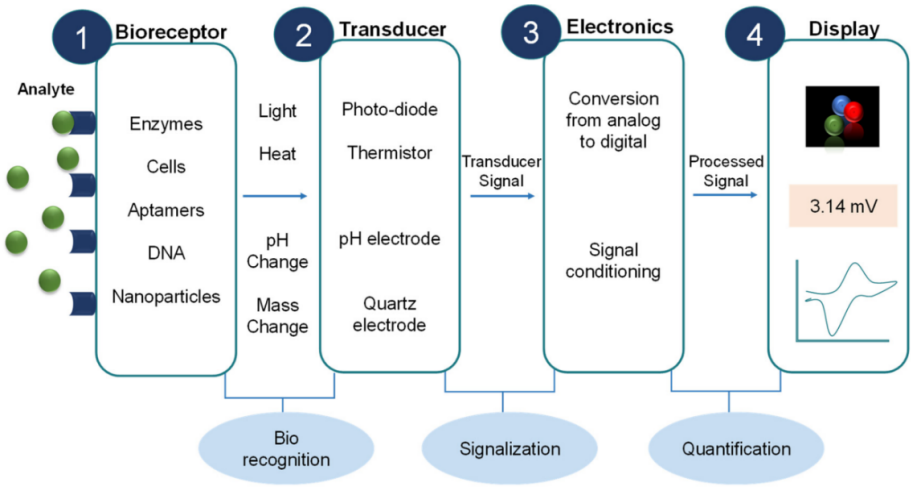

Figure 1. A comprehensive schematic of the biosensor components.

At present, researchers are focused on enhancing the sensitivity and specificity of biosensor technologies by emphasizing the advancement and refinement of fabrication methods. This involves expanding the interaction range through the creation of innovative surface chemistries and the utilization of nanomaterials, including nanofilms, nanoparticles, and quantum dots [13], to boost signal amplification.

Although biosensor-based immunoassays enable more sensitive detection of pathogen-specific antigens, enhancing overall specificity can be achieved by conducting multiple assays targeting host immunoreactive antibodies, such as those used in serological testing. Serological testing is crucial in managing pandemics and monitoring infectious diseases, as it identifies the presence of immunoglobulins (Ig) in the blood produced by an infected host. This approach complements tests for active infection and provides valuable insights into the dynamics of acquired immunity, helping to estimate virus prevalence. For instance, when a person is infected with SARS-CoV-2, their immune system swiftly responds, and antibodies can be detected via serological testing.

The process of antibody production by the human immune system unfolds as follows: Initially, IgM antibodies appear during the acute phase of infection, and after several days or even months, IgM levels gradually decline. Subsequently, the immune system generates persistent IgG and IgA antibodies. IgM antibodies are the first to be produced, offering quick but temporary protection against disease. These antibodies play a key role in immune regulation and tolerance [14]. By binding to antigens, they trigger various responses within the body, initiating the fight against the invading pathogen. In the early stages of infection, the systematic integration of assays that combine pathogen-specific targets with biomarkers reflecting the host's immune response could further advance diagnostic capabilities.

3. Classification of biosensors

Biosensors can be categorized from various perspectives:

(1) Biological Substances for Receptors: Based on the type of biological substance used as a receptor, biosensors are classified into categories such as microbial

sensors, immune sensors, tissue sensors, cell sensors, enzyme sensors, DNA sensors, and others [15].

(2) Detection Principles: Depending on the detection principle of the sensor device, biosensors are categorized into types such as thermal biosensors, field effect transistor biosensors, piezoelectric biosensors, optical biosensors, acoustic biosensors, enzyme electrode biosensors, mesoporous biosensors, and more.

(3) Interaction Type: According to the nature of the interaction between biosensitive substances, biosensors can be divided into two main categories: affinity-based and metabolic-based.

An overview of these categories is illustrated (**Figure 2**) [16].

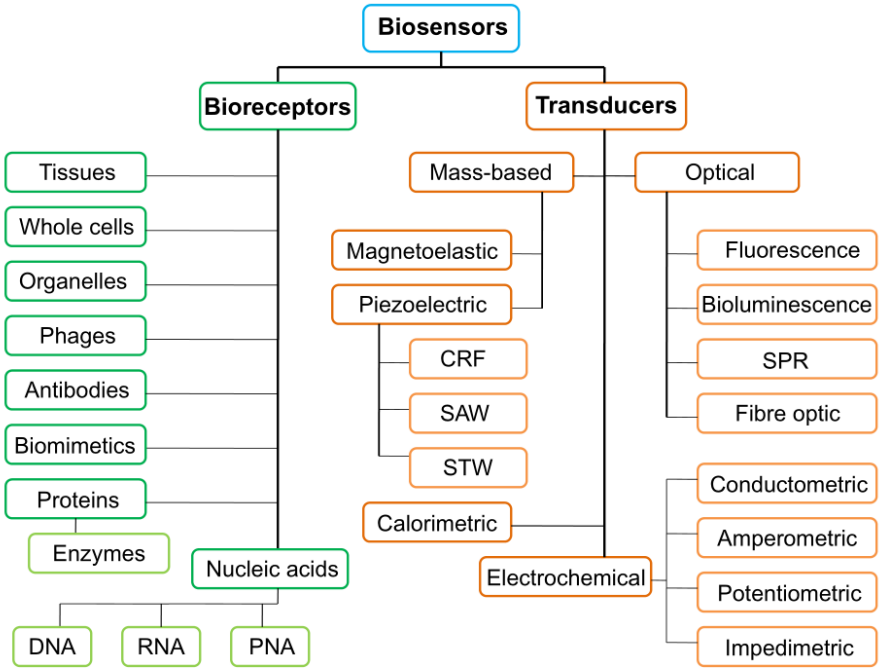

Figure 2. Classification of biosensors based on biorecognition elements and transducers.

Optical sensors are characterized by their high detection speed, sensitivity, robustness, and their ability to detect multiple analytes, such as the surface plasmon resonance (SPR). SPR can determine the presence of a chemical with no need for labeled molecules. SPR sensors, present data by detecting changes in optical signals (e.g., light intensity, color changes).

Mass-sensitive biosensors provide various advantages such as real-time operation. Finally, thermometric biosensors have mainly been employed for monitoring clinical and industrial processes. Biosensors can also be used to detect environmental pollutants, such as heavy metal ions and pesticide residues.

Biomarkers Detected by Biosensors and Their Data Presentation. For example, lung cancer tumor markers NSE and ProGRP31-98 can be sensitively detected using biosensors [17]. In the medical diagnosis field, biosensor technology is applied in glucometers to monitor blood glucose levels in diabetic patients in real-time.

Many biosensors convert biological events into electrical signals for output. For instance, electrochemical biosensors present detection results through changes in

current, voltage, or impedance. In some complex biosensor systems, detection data may be presented in the form of images, such as observing biomolecular interactions through fluorescence imaging or microscopy.

3.1. Microbiological testing

In biosensors, it is evident that the sensitive elements employed include enzymes, microbial bacteria, organelles, animal and plant tissues, antibodies, cells, and DNA. Among these, microbial sensors are the most widely utilized. These biosensors immobilize various living microorganisms onto membranes using cell immobilization technology. The core principle is that the amount of dissolved oxygen consumed or the quantity of electrode-active material produced by the immobilized microorganism remains constant, thereby indicating the quantity of the detected substance.

In the field of mechanobiology, such information is frequently manifested through diverse biological processes, such as cell- extracellular matrices (ECMs) interactions, interactions mediated by cell-cell junctions, cell migration, cellular immune response, and even virus infection of cells (**Figure 3**) [18].

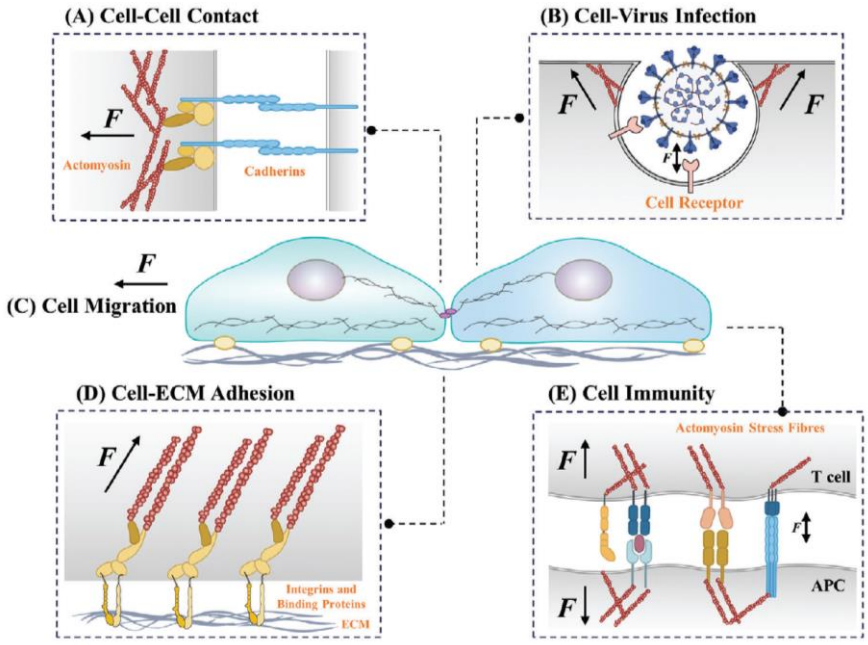

Figure 3. Cell-environment interactions transmit mechanical cues: **(A)** Mechanical information in cell-cell contact; **(B)** Mechanical characteristics of viral infection of cells; **(C)** The guidance of cell migration by mechanical forces; **(D)** Mechanical forces mediated by cell-extracellular matrix interaction; **(E)** Immunoreceptors experience mechanical forces in the immune response.

Microbial sensors are categorized into two types: those that rely on the respiration of microorganisms and those that utilize the enzymes present within the microorganisms. Microbial sensors offer numerous advantages, including high sensitivity, strong selectivity, low production costs, ease of manufacture, and long service life, making them widely applicable [19]. They play a significant role in fundamental theoretical research, clinical testing, industrial product analysis, and environmental quality monitoring. For instance, during glutamic acid fermentation, a

microbial sensor with Escherichia coli as the sensitive element can be combined with a CO_2 gas-sensitive electrode to measure the glutamic acid content. Another example is in sewage testing in Japan, where microbial sensors made from fluorescent Pseudomonas bacteria can determine biochemical oxygen demand (BOD) within 15 min, replacing the traditional 5-day BOD method.

3.2. Enzyme bioassays

Enzyme biosensors consist of substance recognition elements and signal transducers. The key principle behind enzyme biosensors is the use of enzyme-electrode reactions to measure enzyme concentrations. These biosensors serve as analytical instruments, employing enzymes as biosensitive elements and using physical or chemical signal transducers to capture measurable signals generated by the interaction between the target and the sensitive element [20]. The signal is directly proportional to the target's concentration, enabling quantitative detection. Compared to traditional analytical methods, enzyme biosensors feature an immobilized biosensitive membrane integrated with a tightly coupled energy exchange system.

By combining the immobilized enzyme with an electrochemical sensor, enzyme biosensors offer distinct advantages [21]: 1) They leverage the non-invasive nature of enzyme systems and the high sensitivity of electrochemical electrodes. 2) The specific reactivity of enzymes confers high selectivity, allowing direct detection in complex samples. As a result, enzyme biosensors are pivotal in the biosensor industry. Their benefits, such as the high specificity of enzyme-substrate interactions and the high turnover rate of biocatalysts, make enzyme biosensors one of the most extensively studied areas. Based on the enzyme biosensor's sensing principle, the presence of a specific analyte is detected by measuring changes such as proton (H^+) concentration, gas (CO_2, NH_3, O_2, etc.) release or absorption, light emission, reflection or absorption, and thermal emission. These changes occur during substrate consumption or product formation in enzyme reactions. The transducer then converts these changes into a measurable signal—whether electrical, optical, or thermal—to identify the desired analyte [22].

3.3. Protein receptor assay

Protein receptor-based biosensors have emerged as essential tools for detecting biological and chemical analytes due to their high specificity, sensitivity, and versatility. These biosensors capitalize on the natural molecular recognition capabilities of protein receptors to identify target molecules, making them invaluable in fields such as medical diagnostics, environmental monitoring, and food safety. Over the past few decades, significant advancements in materials science, nanotechnology, and bioengineering have propelled the development of these biosensors.

At present, a marker in Pseudomonas A506 using a TN5-based transposon delivery system has been developed. Additionally, it has been demonstrated that green fluorescent protein (GFP) gene expression is sufficient, and fluorescence can be observed under a confocal microscope to monitor different bacterial strains. Detection of cells is based on flow cytometry [23].

Protein receptors serve as biorecognition elements that can identify specific molecules and generate measurable signals. Common types of protein receptor-based biosensors include (**Table 1**) [24]:

Table 1. The type of the protein receptor-based biosensors.

Type	Example	Application
Enzyme Sensors	Glucose Oxidase Sensors	Blood glucose monitoring
Antibody Sensors	Coronavirus Antibody Sensors	Pathogen detection
Aptamer Sensors	Heavy Metal Ion Sensors	Environmental Monitoring
Cell Membrane receptor Sensors	Dopamine Sensors	Neuroscience research
Chimeric antigen receptor Sensors	CAR-T cell Sensor	Cancer immunotherapy
Synthetic Protein Receptor Sensors	Synthetic antibody mimic Sensors	Drug screening, Pathogen Detection
CRISPR-Cas System Sensors	CRISPR-Cas12/13 nucleic acid Sensors	Pathogen and genetic testing

3.4. Immunologic testing

Immunosensors are a type of biosensor that relies on the specific recognition of antigens and antibodies, offering high sensitivity, strong specificity, ease of use, and low cost. The greatest advantage of immunosensors is the high specificity of antigen-antibody binding, which minimizes non-specific interference. Immunosensors incorporate a precision transducer that digitizes the output, enabling not only quantitative detection but also real-time observation of antigen-antibody reactions on the sensor surface due to synchronized energy transfer [25]. This advancement has improved sensitivity, lowered detection limits, and promoted the development of immunodiagnostic methods towards automation and quantitative analysis. The advantages of immunosensors include reduced analysis time, simplified processes, straightforward equipment, and automation.

The most renowned immunosensor is the ELISA, commonly used for clinical protein biomarker detection. Although ELISA is a widely adopted diagnostic tool, its application in rapid diagnostics is limited by the high costs of test kits and plate readers. Hospital laboratories utilize various commercial analyzers such as Luminex, Myriad RBM, Roche Diagnostics, Mesoscale Discovery, Horiba Inc., and BIO-RAD, which employ techniques like fluorescence, electrochemical luminescence, or surface plasmon resonance to perform multiple protein measurements [26]. However, these devices require specialized consumables, such as sample well plates, chips, and kits, making them impractical for expensive, resource-limited point-of-care (POC) applications.

In addition to enzymes, immunosensors also use other labels such as fluorescent reagents like rhodamine, fluorescein, Cy5, and ruthenium diamine complexes, as well as electroactive compounds like ferrocene or In^{2+} salts. Metal nanoparticles, particularly gold or silver produced via in situ electrochemistry, have also gained significant attention recently [27].

3.5. DNA-aptamers-based testing

In recent years, DNA target detection has garnered increasing attention due to its applications across various fields. While traditional DNA detection methods can effectively and accurately identify relevant targets, they often require expensive and bulky professional instruments, involve complex and tedious technical operations, and necessitate skilled personnel, making them unsuitable for real-time or field detection. DNA-aptamers-based biosensors are a newly developed molecular detection technology that relies on the complementary pairing between DNA molecular probes and target DNA to detect and analyze nucleic acids.

DNA-aptamers-based biosensors have rapidly advanced due to their high specificity, quick detection, strong operability, and convenience. Aptamers are defined as small single-stranded DNA (ssDNA) or ribonucleic acid (RNA) sequences of approximately 100 nucleotides or fewer (**Figure 4**) [28]. Currently, optical, mass, and electrochemical DNA biosensors are the main types under research and application, although they have certain limitations. For example, the quartz crystal microbalance DNA biosensor struggles to eliminate the effects of water and gas adsorption on detection sensitivity in meteorological environments. Fluorescent labeling of DNA matrix microarray probes is complicated and costly, potentially affecting probe hybridization efficiency and thus the detection performance. Additionally, fluorescent labeling can suffer from issues like photobleaching and fluorescence quenching.

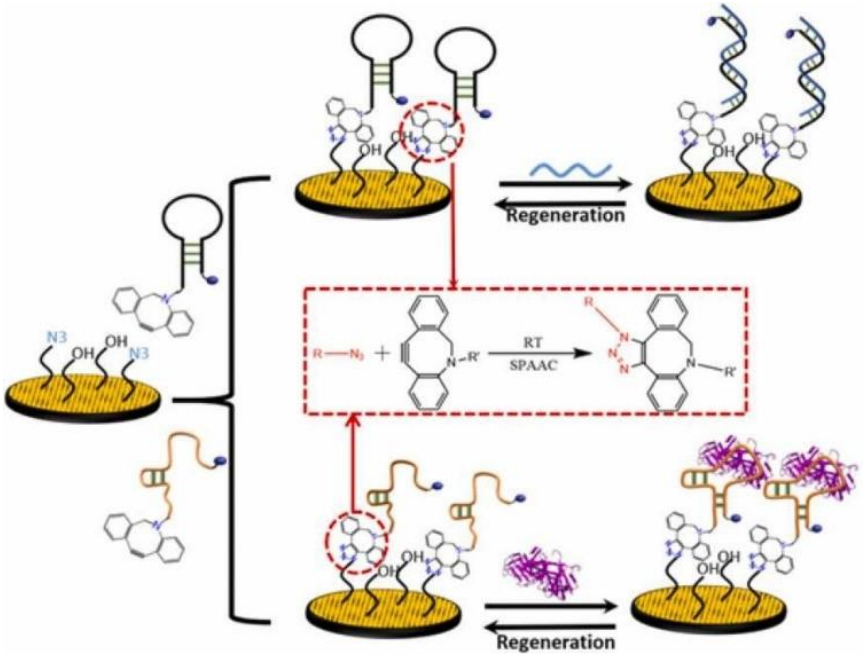

Figure 4. E-DNA/aptamer sensors were constructed using copper-free strain-promoted azide-alkyne cycloaddition (SPAAC) on screen-printed carbon electrodes (SPCE).

Liquid crystals are a unique material with properties such as liquid fluidity, crystal anisotropy, optical anisotropy, and dielectric anisotropy. The application of liquid crystals in biosensors has become a recent research focus. They act as signal amplifiers and transducers in biosensors, enabling sensitive detection of target analytes

without complex instruments, and often without requiring electrical energy. Liquid crystal-based biosensors have been employed for analyzing proteins, antigen-antibody interactions, nucleic acids, bacteria, and viruses [29]. According to literature, most liquid crystal DNA biosensors require both the DNA molecule and the substrate to be modified for probe fixation, which relies on specific recognition between groups. Although this modified fixation method has proven effective in constructing liquid crystal biosensors, challenges remain in precisely controlling the orientation, configuration, and density of surface-fixed probes. These issues, in turn, affect sensor reproducibility, background response, and the hybridization capability of probes, ultimately impacting sensor responsiveness.

4. Recent applications and research

Parasites, bacteria, viruses, and fungi are the primary causes of various infectious diseases, which differ in severity and lead to varying rates of morbidity and mortality among patients. In recent years, global mortality related to infectious diseases has declined due to improved and intensified health measures. However, the threat posed by emerging and recurring diseases caused by new, unknown, or persistent infectious agents remains as significant as ever, particularly in the current unpredictable climate [30]. Many infections are highly contagious, with the potential to spread rapidly and cause epidemics or even pandemics. Therefore, having rapid and portable pathogen detection tools is crucial in addressing this challenge. Quickly differentiating between bacterial and viral infections is essential for accurate diagnosis and effective disease management, helping to prevent the overuse of antibiotics and reduce antibiotic resistance. Accurate and swift diagnosis can also decrease the need for hospitalization or shorten hospital stays, potentially leading to significant healthcare cost savings. However, many current diagnostic methods rely on microscopy, cell culture, nucleic acid amplification tests, or serological methods, which are often time-consuming [31]. The development of portable diagnostic devices that can be easily used in healthcare settings or at home offers the potential for rapid diagnosis of various infections.

4.1. Bacterial pathogens

Human-related bacterial infections, particularly those caused by Gram-negative microorganisms, pose a significant challenge to global health. Various biometric components and nanomaterials are utilized in the development of biosensors for detecting bacteria and antibiotics [32]. Pathogenic bacteria such as Salmonella typhi, Shigella spp., Clostridium perfringens, and Escherichia coli can cause a broad spectrum of diseases in plants, animals, and humans. However, Staphylococcus aureus is often regarded as one of the most dangerous bacteria, known for causing rapidly fatal infections and frequently developing resistance to multiple antimicrobial agents. Consequently, there is an urgent need to develop new methods for its quick and easy detection.

Recently, biosensors have been created to detect pathogenic bacteria. For example, Suaifan et al [33]. developed a biosensor capable of detecting Staphylococcus aureus within minutes. This sensing device relies on the proteolytic activity of a pathogen protease acting on a specific peptide substrate positioned

between two magnetic nanobeads. The dissociation of the magnetic nanobeads-peptide complex results in a color change. Starodub et al. designed a highly specific biosensor for Salmonella detection using SPR and total internal reflection ellipsometry (TIRE). These devices incorporate a surface binding layer and Ag-Ab reaction as the sensing mechanism. The sensitivity of SPR biosensors has been reported to range from 10^1 to 10^6 cells/mL, while TIRE demonstrates even greater sensitivity, detecting as few as a few cells in 10 mL. Narmani et al. [34] developed an ultra-sensitive and selective fluorescent DNA biosensor using AuNPs and magnetic NPs to detect the bacterial O1 OmpW gene (**Figure 5**). Additionally, Shaw et al. embedded a DNA probe through covalent bonding on a fiber-optic biosensor, allowing it to hybridize with fluorescent-labeled complementary DNA. The results are comparable to those obtained through PCR, suggesting this method could serve as an alternative for detecting Shigella.

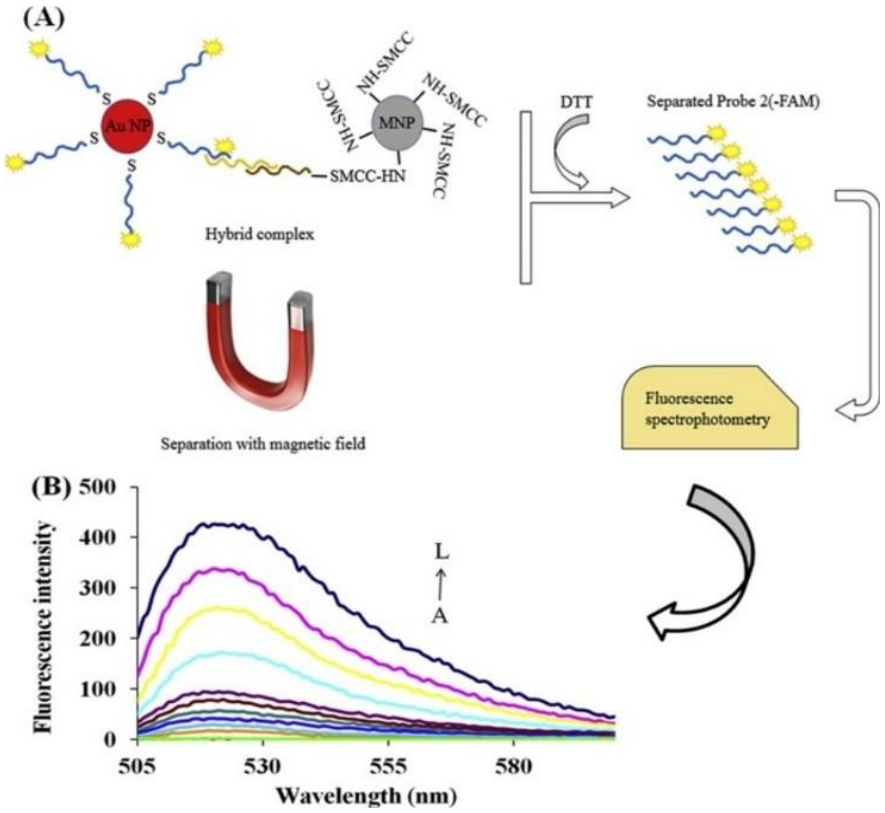

Figure 5. Fluorescence DNA biosensor based on gold and magnetic nanoparticles.

4.2. Viral pathogen

The diagnosis of viral pathogens is vital for effective treatment and preventing the spread of outbreaks or pandemics. Biosensors are increasingly used in diagnostics to enhance efficiency and convenience, eliminating the need for complex protein or nucleic acid recognition techniques specific to certain viruses. The influenza virus, known for its high transmissibility and continuous mutation, is one of the most common and dangerous viral pathogens, making early detection critical.

Sayhi et al. [35] developed an innovative approach for detecting and isolating the H_9N_2 subtype of the influenza A virus. This method involves attaching anti-matrix protein2 antibodies to ferromagnetic nanoparticles, which separate the influenza virus

from the urinary fluid. Gold nanoparticles labeled for electrochemical detection are then attached to fetoglobulin A to detect the viral adhesion properties of the hemagglutinin-fetoglobulin interaction. The complex formed is isolated and treated with an acid solution, which recovers the gold nanoparticles and deposits them on a screen-printed carbon electrode. The biosensor developed by Sayhi et al. was able to detect the influenza virus A/H_9N_2 rapidly, even at a hemagglutination unit (HAU) titer of less than 16. Additionally, Lee et al. created a label-free local SPR biosensor to detect H5N1, achieving a detection limit (LOD) of 1 pM (10^{-12} M). This device features a multifunctional DNA 3-way junction attached to a hollow gold spike nanoparticle, which demonstrates sufficient target recognition and signal amplification capabilities [36].

Other viral pathogens impacting global populations include Human immunodeficiency viruses (HIV), Dengue, hantavirus, and Ebola virus. The Ebola virus, a member of the Filoviridae family, is a negative-strand RNA virus responsible for the deadly Ebola disease. The largest outbreak of Ebola in 2014 led to 15,935 reported cases and 5689 deaths. Despite no current vaccine or specific treatment for this virus, researchers have developed biosensors for its detection. Ilkhani et al. designed a new DNA biosensor using electrochemistry and enzymatic amplification to enhance the device's sensitivity and selectivity [37]. Biotinylated heterozygotes labeled with streptavidin-alkaline phosphatase complexes were optimized using electrochemical impedance spectroscopy, resulting in a low detection limit of 7 nM. The reproducibility and selectivity of this electrochemical biosensor were also assessed. Similarly, Cai et al. conducted studies on the unamplified detection and quantification of the Ebola virus in clinical samples, demonstrating a low detection limit of 0.2 pfu/mL [38].

HIV, a retrovirus that attacks the human immune system, leads to a severe condition if not managed with medication. According to the World Health Organization, over 35 million people have been infected with HIV to date. Early diagnosis and clinical treatment are crucial for reducing mortality and transmission rates. HIV-1, the most prevalent strain of the virus, causes this disease. Shafiei et al. developed a photonic crystal biosensor capable of detecting multiple HIV-1 subtypes (A, B, D) by integrating bioanalyte and biosensor technologies [39]. Lu et al. similarly designed a biosensor to detect HIV-1-related Gp41 by modifying the surface of a quartz crystal microbalance biosensor with a synthetic peptide similar to residues 579–613 of Gp41 via epitope imprinting. This imprinted membrane exhibited a strong affinity for the target peptide and selectively bound to the Gp41 protein [40].

Hantavirus, a group of viruses within the Bunyaviridae family, spreads through contact with fluids, food, or surfaces contaminated with rodent excreta. Gogola et al. conducted a significant study on developing biological transducers, creating an electrochemical immunosensor through the chemical modification of a gold surface by viral antigens/proteins (**Figure 6**) [41]. Additionally, biochar-based electrochemical biosensors are gaining popularity due to their highly functionalized surfaces, which can be covalently bonded to biomolecules, making them a versatile and efficient platform for immunoassay applications.

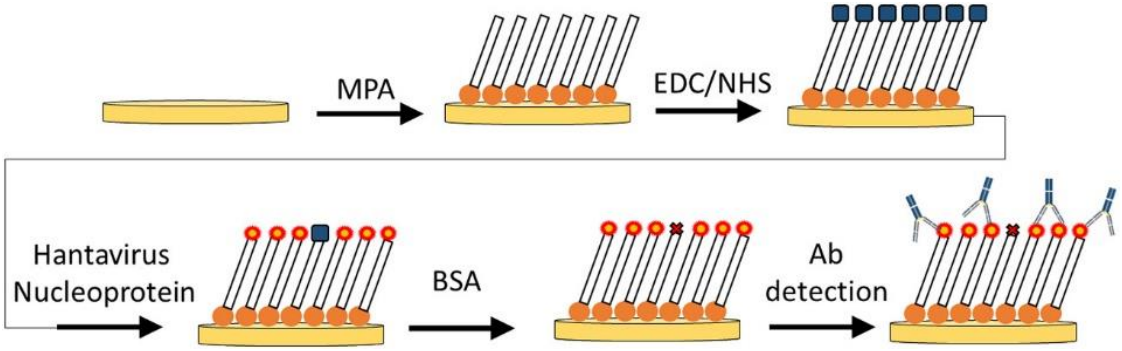

Figure 6. Steps for immunosensor assembly and detection of antibody.

Dengue fever remains a major public health issue globally, caused by the Flavivirus, a single-stranded RNA virus that impacts the human visceral and central nervous systems. Common diagnostic methods for dengue virus infection include serological tests for immunoglobulin M (IgM) and dengue-specific nonstructural 1 (NS1) antigens, using rapid diagnostic tests and ELISA techniques. For example, Lim et al. employed multivalent phages to evaluate the affinity of peptides for the non-structural protein 1 **(**NS1) protein [42]. Among the peptides tested, those that bound to the NS1 protein resulted in significant changes in the electrochemical impedance spectrum, including notable current drops and impedance increases during cyclic voltammetry.

The COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, has resulted in one of the most severe infectious disease outbreaks in human history. Symptoms of COVID-19 can vary widely, including fever, cough, fatigue, shortness of breath, and loss of taste and smell, with an incubation period of 1 to 14 days. At least one-third of infected individuals remain asymptomatic. Among those who do exhibit symptoms, 81% experience mild to moderate symptoms (such as mild pneumonia), 14% suffer from severe symptoms (including dyspnea and hypoxia), and 5% face critical conditions (such as respiratory failure, shock, or multiple organ failure). Elderly individuals are particularly at risk for severe outcomes, and some may experience lasting organ damage. Ongoing studies aim to understand the long-term effects of COVID-19. Early diagnosis is essential for controlling the spread of the virus. Although reverse transcription PCR (RT-PCR) remains the most reliable method for detecting SARS-CoV-2, it is time-consuming and not ideal for remote settings. Therefore, the development of point-of-care (POC) devices for rapid detection is crucial, despite the availability of other methods such as immunoassays, chest imaging, portable x-rays, and amplification techniques. According to Sheridan, there are two primary types of rapid POC biosensors for COVID-19 detection: nucleic acid detection, which identifies the virus in patient samples such as sputum, saliva, or nasal secretions, and antibody tests, which detect the presence of IgM and IgG antibodies produced in response to the virus, typically analyzed from blood samples collected five days post-infection [43] (**Figure 7**).

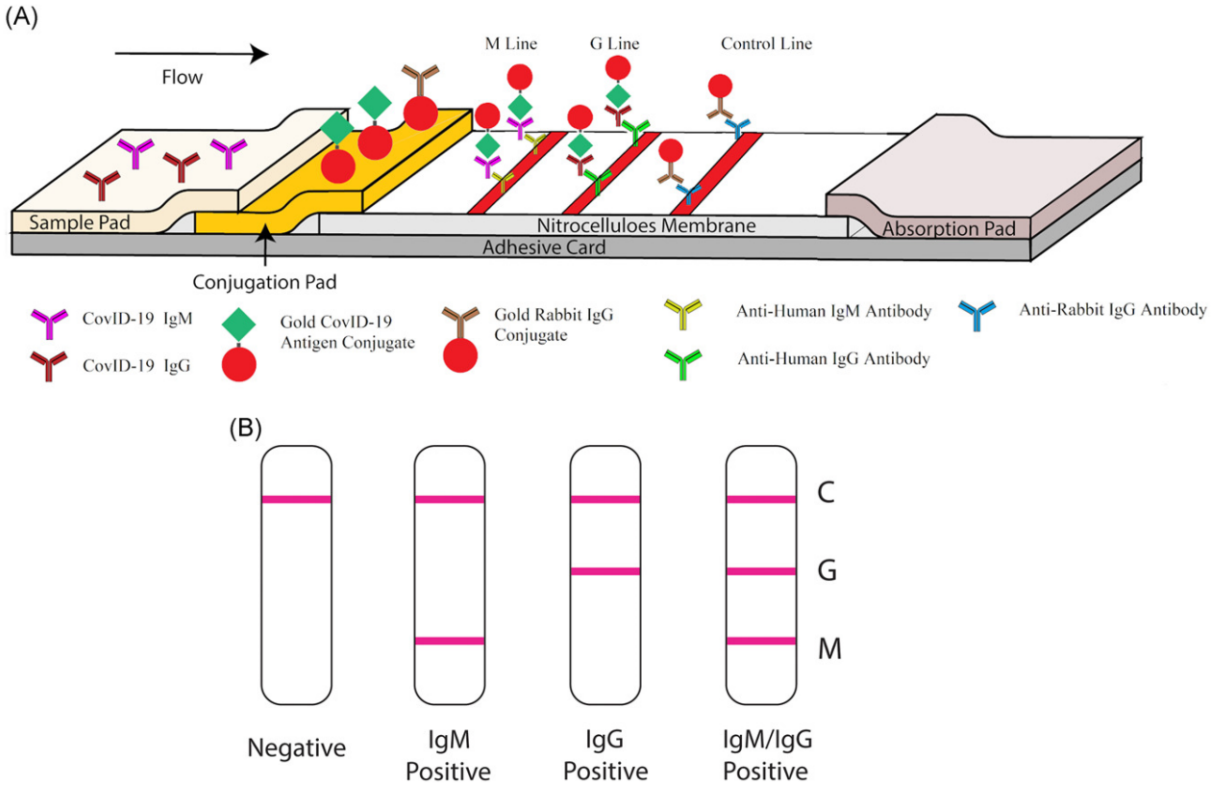

Figure 7. Rapid SARS-CoV-2 IgM-IgG combined antibody test: **(A)** Schematic diagram of the detection device; **(B)** an illustration of different testing results.

Notes: C, means control line; G, means IgG line; M, means IgM line.
IgG, immunoglobulin G; IgM, immunoglobulin M;
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

5. Conclusions

Large-scale automated clinical analyzers in centralized laboratories are commonly employed for testing specific biomarkers, utilizing methods such as nucleic acid or protein microarrays to diagnose infectious diseases. These multiplexed assays typically require highly trained personnel, extensive time, and substantial effort to process multiple analytes. Recent advancements in biotechnology and materials science, however, have led to the development of novel biosensing devices for clinical use, capable of detecting a wide array of biomolecules, including hormones, proteins, nucleic acids, cells, bacteria, and viruses. Biosensors offer numerous benefits, including high stability, reliability, efficiency, cost-effectiveness, and ease of use. While many biosensor platforms are still under development, none has yet emerged as a definitive leader in routine clinical practice [44]. Optimize biosensors to better detect biological signals and improve the effectiveness of infectious disease detection. High-performance biosensors must integrate advanced components with user-friendly designs to meet diverse diagnostic needs. Recent advancements in material science have facilitated the development of innovative portable biosensor prototypes. However, future research should prioritize enhancing the stability of these biosensors' biometric elements under real-world conditions. Environmental factors such as ionic strength, temperature, pH, and viscosity can significantly affect the binding activities of biometric elements.

Additionally, the advancement of multifunctional biosensors is crucial. This involves designing array systems that utilize various bioreceptors for the simultaneous detection of multiple diseases. The increasing demand for rapid and reliable detection presents new challenges for traditional biosensor technologies [45]. For example, the detection of rapidly evolving infectious viruses necessitates biosensors that can quickly adapt and update. Similarly, for comprehensive tumor biomarker screening across multiple loci, biosensors need to incorporate intelligent analysis and programmable capabilities. Furthermore, long-term monitoring applications require biosensors with integrated memory and storage functions.

(1) Portable Biosensors for Point-of-Care Testing (POCT)

The development of Point-of-Care Testing (POCT) technology has enabled portable biosensors to be widely used for on-site detection. Researchers have developed biosensors based on devices such as glucometers, smartphones, and colorimetric test strips to rapidly detect specific target substances. However, challenges remain in terms of portability, miniaturization, and integration of these devices [46,47].

(2) Research Progress on Black Silicon SERS Biosensors

Surface-Enhanced Raman Scattering (SERS) technology has made significant progress in the field of biosensors. Black silicon, due to its unique surface microstructure, has been utilized to fabricate efficient SERS biosensors. Researchers have explored the fabrication methods and surface morphology design of black silicon SERS biosensors, as well as their potential applications in enhancing detection sensitivity [48,49].

(3) Application of Electrochemical Biosensors in Exosome Detection

Exosomes, as important carriers of intercellular communication, play a crucial role in disease diagnosis. Electrochemical biosensors, known for their high sensitivity and specificity, are widely used for exosome detection. Researchers have reviewed the latest advancements in electrochemical sensor-based exosome detection methods, including target selection, biorecognition strategies, and signal transduction mechanisms [47,48].

(4) Trends in Miniaturized and Quantum Biosensors Based on Plasmonics

Plasmonics and Surface Plasmon Resonance (SPR) technologies are widely applied in biosensors. In recent years, researchers have focused on integrating plasmonics into microsystems and lab-on-a-chip platforms to achieve miniaturized and high-sensitivity biosensing [44]. Additionally, research in quantum plasmonic sensing technologies is emerging, aiming to surpass the detection limits of traditional sensors [46,49].

To address these evolving requirements, biosensor development is increasingly focusing on enhancing intelligence and adaptability to meet diverse diagnostic and monitoring needs [50].

Author contributions: Conceptualization, HZ and NSL; methodology, HZ and BX; software, HZ and BX; validation, HZ, BX and NSL; formal analysis, HZ and BX; investigation, HZ and BX; resources, HZ and BX; data curation, HZ and BX; writing—original draft preparation, HZ; writing—review and editing, HZ, BX and NSL; visualization, HZ and BX; supervision, NSL; project administration, NSL;

funding acquisition, NSL. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by Ministry of Higher Education Malaysia through the Higher Institution Centre of Excellence (HICoE) (Grant No.: 311/CIPPM/4401005) and the Fundamental Research Grant Scheme (Grant No.: FRGS/1/2023/SKK06/USM/02/6) to NSL.

Ethical approval: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

References

1. Nutsch K, Song L, Chen E, et al. A covalent inhibitor of the YAP–TEAD transcriptional complex identified by high-throughput screening. RSC Chemical Biology. 2023; 4(11): 894-905. doi: 10.1039/d3cb00044c
2. Timothy A. Bates K. et al. Biolayer interferometry for measuring the kinetics of protein–protein interactions and nanobody binding. Nature Protocols. 2024. doi: 10.1038/s41596-024-01079-8
3. Horner PJ, et al. Chlamydia detection methods: Challenges and future directions. Clinical Microbiology and Infection; 2021.
4. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020; 25(3). doi: 10.2807/1560-7917.es.2020.25.3.2000045
5. Ishita Saha, Neelanjana Bag，et al. The state-of-the-art therapeutic paradigms against sepsis. Smart Materials in Medicine Volume 5, Issue 3, September 2024, Pages 425-446
6. Wang Y, Shi L, Zhu J, et al. Visual and sensitive detection of telomerase activity via hydrogen peroxide test strip. Biosensors and Bioelectronics. 2020; 156: 112132. doi: 10.1016/j.bios.2020.112132
7. Liu ZQ, Qi YX. The progress in nuclear biomechanics. Advances in Mechanics. 2024; 54(2): 259-307. doi: 10.6052/1000-0992-23-053
8. Kalukula Y, Stephens AD, Lammerding J, et al. Mechanics and functional consequences of nuclear deformations. Nature Reviews Molecular Cell Biology. 2022; 23(9): 583-602. doi: 10.1038/s41580-022-00480-z
9. Roumeliotis KI, Tselikas ND. ChatGPT and Open-AI Models: A Preliminary Review. Future Internet. 2023; 15(6): 192. doi: 10.3390/fi15060192
10. Zhang H, Zhao GQ, Feng JT, Lin M. Cellular mechanobiology: Mediated by force-sensitive adhesion receptors. Advances in Mechanics. 2023; 53(1): 48-153. doi: 10.6052/1000-0992-22-029
11. Flynn CD, Sandomierski M, Kim K, et al. Electrochemical Detection of Borrelia burgdorferi Using a Biomimetic Flow Cell System. ACS Measurement Science Au. 2023; 3(3): 208-216. doi: 10.1021/acsmeasuresciau.3c00004
12. Ling Q, Fan X, Ling M, et al. Collagen-Based Organohydrogel Strain Sensor with Self-Healing and Adhesive Properties for Detecting Human Motion. ACS Applied Materials & Interfaces. 2023; 15(9): 12350-12362. doi: 10.1021/acsami.2c21566
13. Liu Z, Mao S, Hu Y, et al. Hydrogel platform facilitating astrocytic differentiation through cell mechanosensing and YAP-mediated transcription. Materials Today Bio. 2023; 22: 100735. doi: 10.1016/j.mtbio.2023.100735
14. Flynn CD, Chang D, Mahmud A, et al. Biomolecular sensors for advanced physiological monitoring. Nature Reviews Bioengineering. 2023; 1(8): 560-575. doi: 10.1038/s44222-023-00067-z
15. Vahabikashi A, Adam SA, Medalia O, et al. Nuclear lamins: Structure and function in mechanobiology. APL Bioengineering. 2022; 6(1). doi: 10.1063/5.0082656
16. Morais PV, Gomes VF, Silva ACA, et al. Nanofilm of ZnO nanocrystals/carbon nanotubes as biocompatible layer for enzymatic biosensors in capacitive field-effect devices. Journal of Materials Science. 2017; 52(20): 12314-12325. doi: 10.1007/s10853-017-1369-y
17. Chen X, Tang K, Li X, et al. Biomechanics of cancer stem cells. Essays in Biochemistry. 2022; 66(4): 359-369. doi: 10.1042/ebc20220014
18. Luo Q, Huang M, Liang C, et al. All-optical Mechanobiology Interrogation of Yes-associated Protein in Human Cancer and Normal Cells using a Multi-functional System. Journal of Visualized Experiments. 2021; (178). doi: 10.3791/62934-v

19. Alhadrami HA. Biosensors: Classifications, medical applications, and future prospective. Biotechnology and Applied Biochemistry. 2017; 65(3): 497-508. doi: 10.1002/bab.1621
20. Cho IH, Kim DH, Park S. Electrochemical biosensors: perspective on functional nanomaterials for on-site analysis. Biomaterials Research. 2020; 24(1). doi: 10.1186/s40824-019-0181-y
21. Vaidya AM, Annapure US. Enzymes in Biosensors for Food Quality Assessment. Enzymes in Food Biotechnology; 2019. doi: 10.1016/b978-0-12-813280-7.00038-4
22. Piliarik M, Vaisocherová H, Homola J. Surface plasmon resonance biosensing. Methods Mol Biol; 2009.
23. Nguyen HH, Lee SH, Lee UJ, et al. Immobilized Enzymes in Biosensor Applications. Materials. 2019; 12(1): 121. doi: 10.3390/ma12010121
24. Chikkaveeraiah BV, Bhirde AA, Morgan NY, et al. Electrochemical Immunosensors for Detection of Cancer Protein Biomarkers. ACS Nano. 2012; 6(8): 6546-6561. doi: 10.1021/nn3023969
25. Manickam R, Ravichandran J, et al. A Review of Fundamentals, Design Principles, Materials, and Applications. Biosensors. 2023; 13(1), 40. doi: 10.3390/bios13010040
26. Fan J, Yang W. Electrochemical DNA/aptamer biosensors based on SPAAC for detection of DNA and protein. Sensors and Actuators B: Chemical. 2022; 353: 131100. doi: 10.1016/j.snb.2021.131100
27. Chen Y, Lv X, Wang Y, et al. Skin-adhesive lignin-grafted-polyacrylamide/hydroxypropyl cellulose hydrogel sensor for real-time cervical spine bending monitoring in human-machine Interface. International Journal of Biological Macromolecules. 2023; 247: 125833. doi: 10.1016/j.ijbiomac.2023.125833
28. Janeway CA, Travers P, Walport M, et al. The Immune System in Health and Disease, Immunobiology, 5th ed. Garland Science; 2001.
29. Yoo SM, Lee SY. Optical Biosensors for the Detection of Pathogenic Microorganisms. Trends in Biotechnology. 2016; 34(1): 7-25. doi: 10.1016/j.tibtech.2015.09.012
30. Yeşeren Saylan ÖESÜ. An Alternative Medical Diagnosis Method: Biosensors for Virus Detection. Biosensors (Basel); 2019.
31. Majdinasab M, Mishra RK, Tang X, et al. Detection of antibiotics in food: New achievements in the development of biosensors. TrAC Trends in Analytical Chemistry. 2020; 127: 115883. doi: 10.1016/j.trac.2020.115883
32. Rubab M, Shahbaz HM, Olaimat AN, et al. Biosensors for rapid and sensitive detection of Staphylococcus aureus in food. Biosensors and Bioelectronics. 2018; 105: 49-57. doi: 10.1016/j.bios.2018.01.023
33. Suaifan GARY, Alhogail S, Zourob M. Rapid and low-cost biosensor for the detection of Staphylococcus aureus. Biosensors and Bioelectronics. 2017; 90: 230-237. doi: 10.1016/j.bios.2016.11.047
34. Narmani A, Kamali M, Amini B, et al. Highly sensitive and accurate detection of Vibrio cholera O1 OmpW gene by fluorescence DNA biosensor based on gold and magnetic nanoparticles. Process Biochemistry. 2018; 65: 46-54. doi: 10.1016/j.procbio.2017.10.009
35. Sayhi M, Ouerghi O, Belgacem K, et al. Electrochemical detection of influenza virus H9N2 based on both immunomagnetic extraction and gold catalysis using an immobilization-free screen printed carbon microelectrode. Biosensors and Bioelectronics. 2018; 107: 170-177. doi: 10.1016/j.bios.2018.02.018
36. Lee T, Kim GH, Kim SM, et al. Label-free localized surface plasmon resonance biosensor composed of multi-functional DNA 3 way junction on hollow Au spike-like nanoparticles (HAuSN) for avian influenza virus detection. Colloids and Surfaces B: Biointerfaces. 2019; 182: 110341. doi: 10.1016/j.colsurfb.2019.06.070
37. Kreil TR. Treatment of Ebola Virus Infection with Antibodies from Reconvalescent Donors. Emerging Infectious Diseases. 2015; 21(3): 521-523. doi: 10.3201/eid2103.141838
38. Walldorf JA, Cloessner EA, Hyde TB, et al. Considerations for use of Ebola vaccine during an emergency response. Vaccine. 2019; 37(48): 7190-7200. doi: 10.1016/j.vaccine.2017.08.058
39. Ilkhani H, Farhad S. A novel electrochemical DNA biosensor for Ebola virus detection. Analytical Biochemistry. 2018; 557: 151-155. doi: 10.1016/j.ab.2018.06.010
40. Cai H, Parks JW, Wall TA, et al. Optofluidic analysis system for amplification-free, direct detection of Ebola infection. Scientific Reports. 2015; 5(1). doi: 10.1038/srep14494
41. Nandi S, Mondal A, Roberts A, et al. Biosensor platforms for rapid HIV detection. Advances in Clinical Chemistry; 2020. doi: 10.1016/bs.acc.2020.02.001

42. Shafiee H, Lidstone EA, Jahangir M, et al. Nanostructured Optical Photonic Crystal Biosensor for HIV Viral Load Measurement. Scientific Reports. 2014; 4(1). doi: 10.1038/srep04116
43. Qian S, Chang D, He S, et al. Aptamers from random sequence space: Accomplishments, gaps and future considerations. Analytica Chimica Acta. 2022; 1196: 339511. doi: 10.1016/j.aca.2022.339511
44. Gogola JL, Martins G, Caetano FR, et al. Label-free electrochemical immunosensor for quick detection of anti-hantavirus antibody. Journal of Electroanalytical Chemistry. 2019; 842: 140-145. doi: 10.1016/j.jelechem.2019.04.066
45. Martins G, Gogola JL, Caetano FR, et al. Quick electrochemical immunoassay for hantavirus detection based on biochar platform. Talanta. 2019; 204: 163-171. doi: 10.1016/j.talanta.2019.05.101
46. Parkash O, Shueb R. Diagnosis of Dengue Infection Using Conventional and Biosensor Based Techniques. Viruses. 2015; 7(10): 5410-5427. doi: 10.3390/v7102877
47. Lim JM, Kim JH, Ryu MY, et al. An electrochemical peptide sensor for detection of dengue fever biomarker NS1. Analytica Chimica Acta. 2018; 1026: 109-116. doi: 10.1016/j.aca.2018.04.005
48. Kumar R, Nagpal S, Kaushik S, et al. COVID-19 diagnostic approaches: different roads to the same destination. VirusDisease. 2020; 31(2): 97-105. doi: 10.1007/s13337-020-00599-7
49. Sheridan C. Fast, portable tests come online to curb coronavirus pandemic. Nature Biotechnology. 2020; 38(5): 515-518. doi: 10.1038/d41587-020-00010-2
50. Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. Journal of Medical Virology. 2020; 92(9): 1518-1524. doi: 10.1002/jmv.25727