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A Review of Recent Advancement in Biosensors Development and their Applications

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ABSTRACT

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Biosensors are revolutionary analytical tools that combine sophisticated transduction processes with biological recognition components to detect biomolecules, infections, and environmental pollutants with extreme sensitivity. Innovations in nanomaterials engineering, the integration of artificial intelligence, and downsizing technologies that enable wearable and point-of-care applications have driven recent advancements. This thorough analysis examines state-of-the-art developments in biorecognition techniques, nanomaterial-enhanced signal amplification, sensor transduction principles, and the integration of biosensing with artificial intelligence for real-time data analytics. We emphasize detection limitations spanning from atto-molar to picomolar concentrations by rigorously analyzing the performance metrics of electrochemical, optical, and piezoelectric biosensors across a variety of sample matrices. This study also includes substantial translation obstacles, such as biofouling, standardization difficulties, regulatory procedures, and commercial viability. Prospects for next-generation intelligent biosensing systems are explored along with new applications in environmental surveillance, food safety, customized medicine, and continuous health monitoring. This study offers researchers a thorough road map for developing biosensor technology from lab prototypes to clinical and commercial realities.

Introduction

Biosensors are a new concept in analytical chemistry that involves the specificity of biological identification with the quantitative ability of physical transduction [1]. Current developments have been based on simple glucose biosensing with enzyme electrodes, building upon the pioneering work of Clark and Lyons in 1962. Current technologies have advanced to multimodal biosensing systems with the capability to multiplex the detection system, wireless transmission, and independent decision-making [2]. Biosensors are gadgets, which determine the level of expression of indicators through the combination of analytes, receptors, transducers, and outputs. These diagnostic and analytical tools can work with biological samples (analytes) to extract information using a combination of biological detecting molecules (receptors) and electrical sensor system, which includes a transducer (Figure 1). Biosensors are developed based on target analytes, including DNA, immunological, and cancer markers, present in biological samples. Some of the biosensors include bio-computers, glucometers, biochips, and resonant mirrors [3].

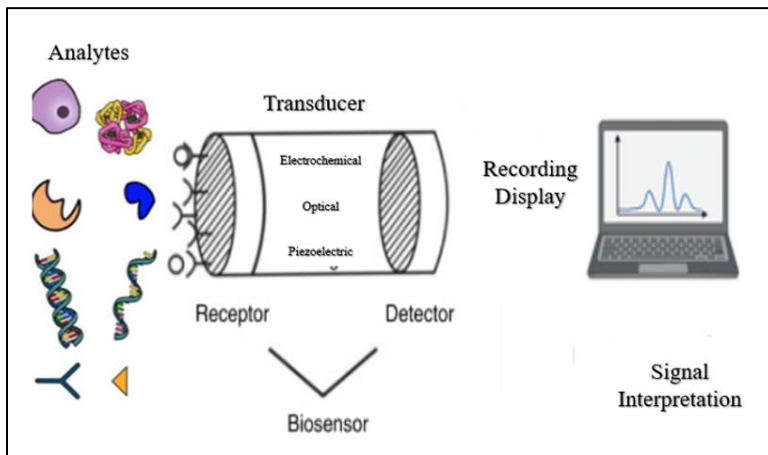


Figure 1 : Elements of Biosensors (Drawn by author)

The most rapidly expanding branches of the global biosensor market, which has been projected to be approximately 23.9 billion dollars in 2020, are wearable biosensors and point-of-care testing. Integration of artificial intelligence to pattern recognition and predictive analytics [5] and development of flexible electronics that can be easily integrated with the human body [6]. By 2027, the market will have expanded to reach 54.7 billion. This exponential yearly growth can be attributed to the increase in the demand of environmental surveillance, food safety assurance, customized treatment, and continuous health monitoring.

The review analyzes the recent advances in six key areas: (1) mechanisms of transduction and optimization of performance; (2) nanomaterial-enabled detection systems; (3) bio-recognition engineering, such as CRISPR-based detection; (4) wearable and point-of-care detection; (5) artificial intelligence integration; and (6) barriers to translation and commercialization opportunities. The latest and most updated literature take precedence with the emphasis on high-impact research indicating commercial implementation, clinical validation or paradigm-shifting technology.

Transduction Mechanisms:

Transduction is the functional basis of present day biosensors and it is capable of converting biological events to quantifiable signals. Electrochemical, optical and piezoelectric transduction have been significantly advanced during the past decade, especially (Figure 2). Nanotechnology, microfluidics, materials engineering and the increasing requirement of point-of-care (POC) diagnostic have contributed to these developments.

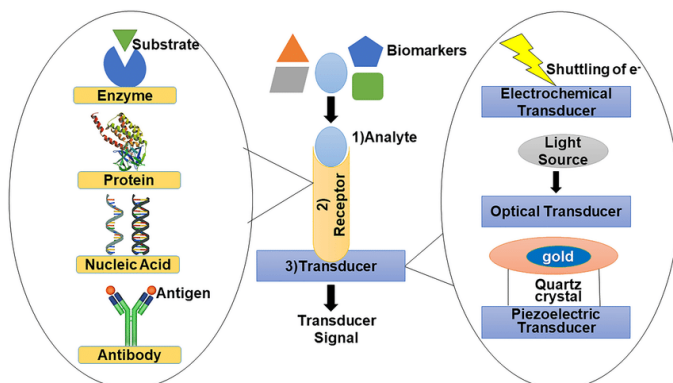


Figure 2: Different Transduction Mechanisms [7]

Electrochemical Transduction

A bio electrochemical component serves as the primary transduction mechanism in biosensing, measuring electrical characteristics to extract information from biological systems. While electrochemical detection methods primarily rely on enzymes, biosensing devices employ a variety of recognition elements (Figure 3). Their unique binding properties and biocatalytic activity are primarily responsible for this. Antibodies, nucleic acids, cells, and microorganisms are examples

of additional biorecognition components. An immunosensor tracks binding events in bio electrochemical processes using antibodies, antibody fragments, or antigens [8]. Due to its low cost, compatibility with miniaturization, and robustness qualities that have enabled successful deployment in glucose monitoring, wearable microfluidic devices, and disposable diagnostic platforms, electrochemical transduction continues to be the most popular method in commercial biosensors [9]. Among the different biosensing modalities are optical, piezoelectric, thermal, magnetic, electrical, and electrochemical. Electrochemical biosensors are unique in that they are inexpensive, simple, and compatible with miniaturized and portable systems.

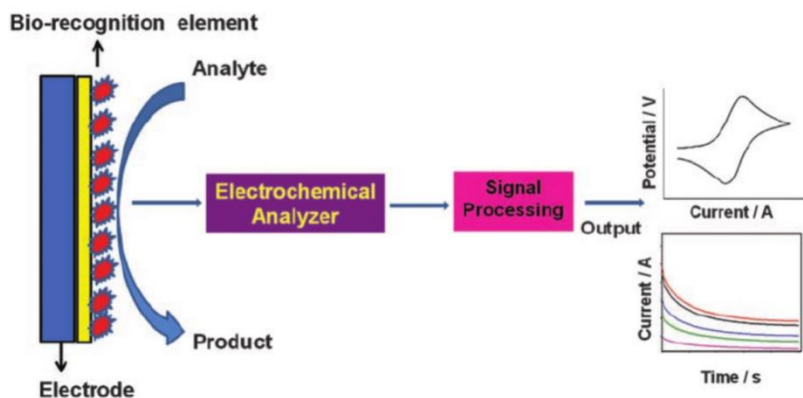


Figure 3: Design of Electrochemical biosensors [10]
Amperometric Biosensors

One of the oldest and most well-known electrochemical techniques is amperometric biosensing, which measures current generated by oxidation or reduction processes at a given potential. This field is still changing due to significant innovations. Direct electron transfer designs have replaced traditional diffusional redox mediators in mediator-based amperometric systems, especially in third-generation platforms. Enzymes like glucose oxidase may directly exchange electrons with electrodes thanks to electrical "bridges" provided by conducting polymers, vertically oriented carbon nanotube arrays, and metallic nanoparticles. In one noteworthy example, aligned CNT arrays with covalently bound glucose oxidase were used to achieve performance parameters that outperformed most commercial sensors, including a sensitivity of $52.3 \mu\text{A mM}^{-1} \text{cm}^{-2}$ and a detection limit of $0.8 \mu\text{M}$ [11].

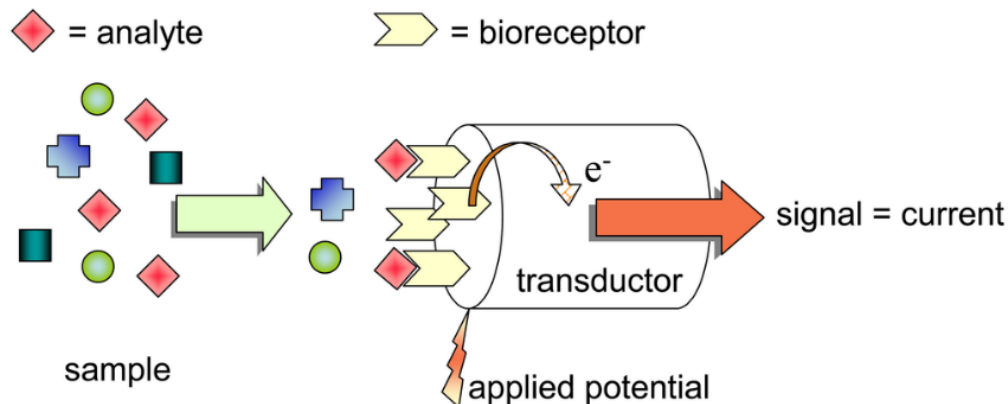


Figure 4: Functional principles of Amperometric bio-sensors [12]

Concurrently, enzymatic and microbial biofuel cell-based self-powered biosensors have created new opportunities for battery-free, autonomous sensing. Recent glucose biofuel cells that deliver more than $100 \mu\text{W cm}^{-2}$ can continuously power low-power wireless modules for real-time glucose monitoring. These systems use biological processes to harvest electrical energy [13]. Microfluidic paper-based electrochemical devices (μPADs) have extended amperometric biosensing to accessible diagnostics in low-resource environments. With a surprising 0.5 pg/mL sensitivity, a 3D-printed

μ PAD that integrated capillary-driven flow and screen-printed electrodes identified cardiac troponin I from unprocessed whole blood [14], highlighting their potential for decentralized healthcare.

Potentiometric Biosensors

An electrochemical method is a potentiometric method in which extremely little bias current (10^{-15}) flows as the potential between a functional electrode is measured relative to a reference electrode. This method has the benefit that it is easy to use, small and power efficient [15].

Ion-selective electrode (ISE)-based potentiometry has long been a popular, low-cost method that may be converted into portable kits [16]. The primary benefits of potentiometric-based sensors are their quick reaction, broad dynamic range (3–5 orders of magnitude), simplicity of use, portability, ease of customisation, and affordability [15]. Recent breakthroughs in this field have enabled the detection of neurotransmitters [6, 7], proteins [8], microorganisms [17, 18], tiny compounds [19, 20], and toxins. Biomimetics have been used as an ion exchanger in polymeric membranes, analyte-selective enzymes have been added to some parts of the biosensor to form ions that an ISE membrane is selective for, and multiple molecule sandwiches made of antibodies, DNA, proteins, or aptamers have been integrated into the polymeric membrane [17, 21]. Recent advancements include a miniaturised solid-state ISE, a combined ISE and FET, and simultaneous potentiometric detection of two analytes [17]. High sensitivity (aM to nM) is being achieved using field-effect transistors (FETs). These transistors work by changing the voltage at the gate electrode, which changes their conductance. Biologically linked FETs (Bio-FETs) bind the analyte to the biorecognition element, altering the semiconductor layer's charge distribution and thereby the device's overall conductance. Bio-FETs offer huge linear ranges, high sensitivity, and can be easily and cheaply downsized [22, 23].

Recent advancements in biosensors include the use of extended gate electrodes [23, 24] to segregate the biorecognition part from the rest of the FET, and a polymeric nano filter to reduce interference from tiny molecules [23]. Researchers are experimenting with FETs based on several concepts, such as junctionless nanowire FET and organic electrochemical transistors, to attain desirable performance levels [25].

Impedimetric Biosensors

Biosensors based on electrochemical impedimetric spectroscopy measure the electrical impedance formed at the electrode/electrolyte interface in response to a tiny sinusoidal stimulus [26]. Electrochemical impedance spectroscopy (EIS) is a promising electrochemical method used in biosensors to assess biocatalytic and electrode changes, as well as the transduction of biosensing events at electrodes [27, 28]. The EIS incorporates information on materials' capacitive and resistive characteristics [29, 30]. Furthermore, because it is a non-destructive procedure that produces high-quality data, it is a valuable tool for biosensor development [31]. The configuration of an EIS system is extremely lightweight and portable. As a result, the analysis can be performed outside of the laboratory [31, 32]. EIS is an essential technique for understanding the properties of specific biorecognition events, such as antigen or antibody capture at the electrode surface, molecular biorecognition of particular proteins, and recognition of receptors, nucleic acids, and even whole cells [33]. However, electrochemical impedimetric biosensors degrade in performance over time and limit current flow. Several techniques have been developed to overcome this effect and improve the signal, including attaching to a variety of labelling molecules such as DNA, enzymes, nanoparticles, and carbon compounds [34]. In the realm of biosensors, several novel modalities have recently been introduced, including aptamers, nanomaterials, and molecularly imprinted polymers (MIPs). [34-36]. Furthermore, developments in nanotechnology have led to the creation of nanomaterials with a high surface-to-volume ratio, which may help biosensors achieve greater sensitivity and efficiency [37]. These cutting-edge biosensing platforms have the potential to make detection faster, more accurate, and more accessible than ever before as the paradigm moves from centralized, research-based analytical and screening techniques to decentralized, point-of-care (PoC) and point-of-need platforms [38].

Despite these developments, there are still several technological and practical obstacles that prevent impedimetric biosensors from being widely used and commercialized. The first is stability and repeatability; many biorecognition components, especially enzymes and antibodies, are susceptible to deterioration over time. Inconsistencies and difficulties with fabrication result from this. It is anticipated that improvements in electronic fabrication processes, micro- and nano-

fabrication techniques, and manufacturing procedures would further develop this class of biosensors by reducing batch-to-batch variation and quality control requirements[39].

Optical Transduction

Plasmonic nanostructures, enhanced nanophotonic, and the incorporation of optical components into consumer electronics have all significantly changed optical transduction. Miniaturization and integration into portable platforms have benefited surface plasmon resonance (SPR), which tracks change in refractive index close to metal surfaces in real time. Gold-coated optical fibers have been utilised in smartphone-interfaced SPR systems to detect cortisol in saliva with a sensitivity of 0.1 ng/mL while preserving a cheap cost (<\$500) and compact form factors appropriate for point-of-care applications [40]. By concentrating electromagnetic fields at the nanoscale, advanced plasmonic nanostructures like gold nano stars, nanorods, and nano islands increase sensitivity by ten to one hundred times. Prostate-specific antigen (PSA) was recently identified at 0.1 pg/mL using a nano star-based technology, outperforming clinically approved ELISA techniques [41]. Fluorescence-based biosensing remains the most widely used method for applications requiring high sensitivity. For the detection of proteins, nucleic acids, and tiny molecules, quantum dots, lanthanide complexes, upconversion nanoparticles, and FRET-based designs are frequently used [42]. While time-resolved fluorescence using lanthanide probes, which have lifetimes in the microsecond range, effectively suppresses autofluorescence in biological tissues, greatly enhancing analytical reliability, ratiometric fluorescence sensors using dual-emission nanoparticle pairs have improved accuracy by removing environmental and instrumental variability [43].

Colorimetric biosensing is still crucial for POC and low-cost applications even if it is less advanced. In this area, nanozyme nanomaterials with catalytic activity that mimic that of enzymes have made considerable progress. While CeO₂ nanoparticles have been used to detect glutathione at 50 nM, enabling the assessment of oxidative stress conditions [41].

By using optical characteristics like local surface plasmon resonance (LSPR), nano plasmonic colorimetric biosensors have recently significantly increased their sensitivity for the detection of trace amounts of analytes [44]. LSPR-based colorimetric research mainly uses noble metal nanoparticles, such as gold (Au) and silver (Ag), and the sensitive LSPR effect is being studied by changing the size, shape, and surrounding environment of these nanoparticles [45]. Additionally, researchers are concentrating on the use of nanomagnets in colorimetric biosensors, which are said to be more stable and reproducible than conventional protein enzymes [46]. Ultimately, it is anticipated that demonstrating a colorimetric biosensor with nanotechnology would improve sensitivity and selectivity, allowing the detection of trace quantities of analytes. By offering speedy results with basic equipment, this might further enhance POCT and expand access to healthcare in disadvantaged areas [47, 48].

Piezoelectric Transduction

Piezoelectric biosensing has evolved into a potent modality for real-time, label-free detection of biomolecular interactions, with quartz crystal microbalance (QCM) and surface acoustic wave (SAW) sensors staying at the heart of mass-based transduction technologies. Through resonant frequency shifts, quartz crystal microbalance (QCM) devices quantify mass changes at the nanogram scale, allowing for a thorough examination of interactions at solid-liquid interfaces [49]. QCM systems have been used to detect viruses, such as influenza A, at 10³ PFU/mL using sialic acid-functionalized surfaces [50]. They have also been used for exosome profiling, where multiplexed detection of cancer-derived exosomes has been accomplished with a sensitivity of about 10² particles/μL [51]. QCM has also helped drug screening applications by allowing kinetic study of protein–ligand interactions with nM affinity precision [52].

Surface acoustic wave (SAW) biosensors have also improved significantly due to their extremely high operating frequencies and remarkable surface sensitivity. SAW devices, such as Love-wave and shear-horizontal setups, may detect minute changes in mass, viscosity, or mechanical stress at the solid-liquid interface, offering up to 10-100× greater sensitivity than typical QCM. Current SAW platforms have been used to detect pathogenic bacteria at very low concentrations, allowing for food safety monitoring and rapid on-site diagnostics. For example, high-frequency SAW chips have been reported to detect *Escherichia coli* with high sensitivity via phase and frequency monitoring [53]. Advanced SAW designs have also shown the potential to detect extremely tiny cell populations, such as circulating malignancy cells, by utilizing improved acoustic confinement and functionalized polymer surface [54].

Recently, piezoelectric hydrogels and hybrid soft-piezoelectric materials have been developed as next-generation transducer platforms, providing flexibility, biocompatibility, and improved mechanical-electrical coupling for biosensing applications. Collectively, these improvements indicate a significant shift toward incorporating innovative materials, microfluidics, and synthetic receptors into piezoelectric biosensors, establishing QCM and SAW technologies as critical components of current diagnostic and environmental monitoring systems.

Nanomaterial-Enhanced Biosensing Platforms

Nanomaterials have become key components of high-performance biosensing over the past 5 years, offering exceptional sensitivity, selectivity, and stability across many transduction mechanisms. High surface-to-volume ratios, tunable surface chemistry, quantum confinement effects, and superior electrical conductivity are among their special qualities that enable efficient biomolecule immobilization, improved electron transfer, and signal amplification all essential for next-generation electrochemical, optical, and piezoelectric sensors.

Carbon-Based Nanomaterials

Graphene, MXenes and carbon nanotubes (CNTs), carbon-based materials that have been used extensively because of their large surface area, remarkable conductivity, and adjustable surface chemistry. Because of its two-dimensional structure and electron mobility exceeding $200,000 \text{ cm}^2/\text{V}\cdot\text{s}$, graphene has been incorporated into wearable and point-of-care devices. Heteroatom doping, laser-engraved porous graphene, and graphene quantum dots have made it possible to detect uric acid ($0.5 \mu\text{M}$), dopamine (10 nM), and glutathione (50 nM) with extreme sensitivity [43, 55, 56].

Table 1: Graphene-based glucose biosensors

Nanomaterial	Transduction Method	Linear Range	Detection Limit	References
Graphene-Gox	Amperometric	0.01-10 mM	$0.8 \mu\text{M}$	[11]
MXene-Gox	Amperometric	0.005-13 mM	$0.5 \mu\text{M}$	[57]
ZnO NRs-Gox	Amperometric	0.5-8 mM	$0.5 \mu\text{M}$	[58]
CuO/GO	Electrochemical	0.0028-2.03 mM	$0.69 \mu\text{M}$	[59]

CNTs provide superior electron transport and high aspect ratios. Sensitive glucose detection ($42.5 \mu\text{A mM}^{-1} \text{ cm}^{-2}$) and cardiac troponin I detection (0.5 pg/mL) have been achieved by vertically aligned CNT forests and functionalized multi-walled CNTs, and real-time lactate monitoring during exercise is made possible by CNT yarns incorporated into textiles [60].

MXenes are two-dimensional transition metal nitrides and carbides, provide quick, label-free detection by combining hydrophilic surfaces with metallic conductivity. Within five minutes, TiOCT-based FET sensors identified COVID-19 nucleocapsid protein at 0.2 fg/mL , while MXene-enzyme composites enhanced glucose sensing sensitivity to $78 \mu\text{A mM}^{-1} \text{ cm}^{-2}$. Moreover, multiplexed sweat analysis with $>90\%$ performance retention after 1000 bend cycles was made possible by flexible MXene electrodes [57, 61].

Metal Nanoparticles

Numerous uses in the biomedical industry have arisen from the ability to produce metal nanoparticles in the same size range as proteins (1 to 100 nm). Their special qualities, such as a high proportion of atoms or molecules on the surface and a large surface-to-volume ratio, can be used to enhance the sensing and detection of several significant biomolecules in domains connected to healthcare. To achieve signal amplification, increased sensitivity, and significant advancements in the detection and quantification of various biomolecules, metal nanoparticles (NPs) can be employed both alone and in conjunction with other nanostructures [62]. The physico-chemical characteristics and alterations that metallic nanoparticles undergo after binding the biomolecular analyte on the surface are actually directly linked to their function in biosensing: (1) they serve as immobilizing platforms; (2) they accelerate electron transfer; (3) they catalyze the chemiluminescent reaction with their substrates; (4) they amplify changes in mass; and (5) they enhance changes in refractive index [63].

Among the most researched nanomaterials are noble metal nanoparticles (NPs), especially gold and silver NPs, which have produced a plethora of methodologies and techniques for drug administration, imaging, molecular diagnostics, and

therapies. Most of their special nanoscale physicochemical characteristics, such Localized Surface Plasmon Resonance (LSPR), have been investigated for the creation of novel biosensors [64].

In a conventional ELISA immunoassay, gold nanoparticles functionalized with an antibody anti-CA15-3-HRP were also used to increase the assay's optical signal and identify a breast cancer biomarker found in blood (i.e., CA15-3 antigen) [65]. The gold NPs-based ELISA demonstrated a greater sensitivity and shorter test time when compared to traditional ELISA techniques, enabling the detection of a target within the 0–60 U/mL range. Additionally, Zhang et al. created a human serum albumin (HSA) immunosensor based on a glass slide coated with chitosan that included a polymer containing amino groups that functioned as anti-HAS antibody coupling sites (using glutaraldehyde) [66]. The sandwich-type immunocomplex was then completed by adding the antigen (HSA) and gold NP-labeled anti-HSA. UV-visible spectroscopy revealed a linear association between the logarithm of HSA concentration and the absorbance intensity. To track dynamic interactions with a particular secondary antibody in real time, Mayer et al. have also investigated changes in the LSPR spectral extinction peak of gold nanorods, and bipyramids NPs linked with antibodies [67].

Palladium NPs and other binary and ternary combinations of metal NPs in oxides, sulfides, or metallic form (Bi₂S₃, ZnO, CuO, Co₃N, Co₃O₄, Ni/ZnO, MoS₂, IrO₂, NiO, TiO₂, PbS, Pd@Pt, Ni-Co@Pt, etc.) with various morphologies (nanowires, nanosheets, nanofibers, nanotubes, nanorods, core-shell, and so on [68, 69]. In addition to their widespread usage as electrode modifications with bioanalytical applications, they can function as electrocatalysts (bimetallic and trimetallic NPs have a synergistic impact) [70]. TiO₂ nanoparticles are given particular consideration because of the following benefits: Since Ti is a biocompatible and plentiful material, TiO₂ nanomaterials are frequently used as a supported material for decoration with other metal NPs with numerous biomedical applications because they are chemically stable, mechanically strong, highly uniform, have a large surface area, have photo-catalytic properties, and have multiple functions [71].

Table 2: List of Nanomaterials based biosensor for the past two decades.

Nanomaterial	Analyte	Transducer	Linear Range	References
Au NPs	Uranyl	Electrochemical	2.4 - 480 $\mu\text{g L}^{-1}$	[72]
Au/CdS QDs/TNTs	Cholesterol	Electrochemical	0.024 -1.2 mM	[73]
Pt NPs/RGO–CS–Fc	H ₂ O ₂	Electrochemical	2.0×10^{-8} M - 3.0×10^{-8} M	[74]
Pt–Fe ₃ O ₄ @C	Sarcosine	Amperometric	0.5 - 60 μM	[75]
Pd/Co-NCNT	Hydrazine	Electrochemical	0.05 -406.045 μM	[76]
Ag@CQDs-rGO	Dopamine	Electrochemical	0.1-300 μM	[77]
Cu NPs/Rutin/MWCNTs/IL/Chit/GCE	H ₂ O ₂	Cyclic Voltammetry	0.35-2500 μM	[78]
Cu ₂ O@CeO ₂ –Au	PSA	Amperometric	0.03 pg mL^{-1}	[79]
Ni/Cu MOF	Glucose	FET	1 μM - 20 mM	[80]
NiO@Au	Lactic acid	Electrochemical	100.0 μM - 0.5 M	[81]
Co ₃ O ₄ –Au	miRNA-141	Photoelectricalchemical	1 pM - 50 nM	[82]
Fe ₂ O ₃ /NiO/Mn ₂ O ₃ NPs	Folic Acid	Electrochemical	0.1 nM - 0.01 mM	[83]
ZnO-rGO	Dopamine	Cyclic Voltammetric	0.1-1500 pM	[84]
Ca/Al–ZnO NPs	CO ₂	Semiconductor	0.25-5 RH%	[85]
TiO ₂ /APTES	Glucose	Impedimetric	50-1000 μmol	[86]
CNT/Au NPs	Choline	Amperometric	0.05-0.8 mM	[87]

Quantum dot-based biosensors

Semiconducting nanocrystalline solids known as quantum dots (QDs) typically have diameters between 2.0 and 10.0 nm[88]. These nanomaterials exhibit varied hues depending on their size, ranging from orange or red for QDs with a diameter of 5.0–6.0 nm to blue or green for smaller QDs with a diameter of 2.0–3.0 nm. The size, shape, and structures of QDs are the primary determinants of their characteristics. Large-sized carbon materials, such as graphite, graphene oxide,

carbon nanotubes, and carbon fibres taken from various sources, are broken down into tiny nano-sized quantum dots using a top-down process, which is one of the primary approaches for the synthesis of QDs. They have been widely employed as alternatives to mimic fluorophores in the construction of optical biosensors for the detection of macromolecules and chemical substances [89].

Table 3: QD-based biosensors utilized to identify different analytes.

Type of QDs	Analyte	Sensor type	Linear Range	References
MoS ₂ /CdTe	Tetracycline	Fluorescence	0.1 - 1 μ M	[90]
ZnCdSQDs@MIP	Ascorbic acid	Fluorescence	1 - 500 μ M	[91]
Polymer CdTe/CdS	Glucose	Fluorescence	0.2 - 5 mM	[92]
CdTeS @SiO ₂	Folic acid	ImageJ software	5 - 80 μ M	[93]
MoS ₂ /GQD	Caffeic acid	Electrochemical	0.38 - 100 μ M	[94]
Ni-doped CdTe	Pyrazinamide	Fluorescence	2 - 100 μ M	[95]

Beyond its use in detecting *Yersinia enterocolitica*, this innovative electrochemical method has the potential to transform clinical and food sample analysis. This technology offers a practical, quick, and economical way to identify various pathogenic bacteria across a variety of sample matrices by eliminating pre-sample treatment. Therefore, the novel GQD-immunosensor has the potential to revolutionize infectious agent diagnosis and detection techniques, which would be advantageous for both clinical and food safety applications [96].

Carbon nanotubes-based biosensors

Carbon nanotubes (CNTs) are the most actively researched class of nanomaterials for the development of biosensors used for various diagnostic applications in medical and other scientific fields, as well as a scaffold for the immobilization of biomolecules on their surfaces. In 2006, Tang et al. developed a single-walled carbon nanotube (SWNT)-based DNA sensor with high sensitivity and responsiveness [97].

Table 4: CNTs-based biosensors with different analytes

Sensor	Analyte	Mechanism	LOD	References
CNTs	Streptavidin	Amperometric	100 aM, 100 -10 ⁶ aM	[98]
	Prostate-Specific antigen	Chemiresistive	1.18 ng/mL, 0 - 1000 ng/mL	[99]
	Formaldehyde	Amperometric	0.016 ppm, 0.05 - 6.7 ppm	[100]
	Tetrahydrocannabinol	Chemiresistive	0.163 ng, 0.0018 - 0.8262 μ g	[101]
	DNA (cDNA from Cancer Cell)	Spin-coat	880 ng/L, 50 - 5 \times 10 ⁶ pM	[102]
	NH ₃	Chemiresistive	2 ppm, 2-40 ppm	[102]
	Ethanol	Chemiresistive	17-70 ppm, 17-70 ppm	[103]

Janssen et al. developed a CNT-based biosensor for detecting bovine serum albumin (BSA) with a good detection limit [104].

Florian et al. made another essential addition to this subject by presenting a unique technique that included the construction and extensive evaluation of fluorescent carbon nanotube-based sensors for neurotransmitter detection [105]. Florian and colleagues used systematic manipulation of the organic phase surrounding single-walled carbon nanotubes (SWCNTs) to create a variety of sensors, each with a unique selectivity and sensitivity profile tailored for catecholamine neurotransmitters. The consequences of this study are significant, as DNA-functionalized SWCNT-based sensors have the potential to transform our ability to investigate neurotransmitter transmission in complex biological

environments. Because of their increased selectivity and sensitivity, these sensors have the potential to be invaluable tools in deciphering the intricate interplay of neurotransmitters in both health and disease contexts, paving the way for unprecedented levels of detail in understanding the complexities of neurological processes [96].

Table 5: Advanced Nanomaterial based biosensors.

Nanomaterial	Target Analyte	Detection Limit	Sensor	Reference
Laser-engraved graphene	Uric acid in sweat	0.5 μM	Wearable electrochemical sensor	[55]
N-doped graphene	Dopamine	10 nM	Electrochemical detection	[56]
Graphene quantum dots	Glutathione	50 nM	Dual electrochemical/optical	[43]
Functionalized MWCNTs	Troponin I	0.5 pg/mL	Cardiac troponin I sensor	[60]

Bio-Recognition Elements

Bio-recognition element employed in biosensors determines their performance, selectivity, and therapeutic usefulness. Significant advancements in natural, designed, and synthetic recognition systems occurred between 2020 and 2025, moving biosensing away from conventional formats based on enzymes or antibodies toward more reliable, scalable, and programmable biointerfaces. Bioengineering, nucleic acid nanotechnology, computational protein design, and nanomaterial–biomolecule hybridization were the main drivers of these developments.

Enzymatic Biosensors

The performance of biosensors was further improved by antibodies and modified affinity proteins, with monoclonal antibodies remaining the most popular due to their high affinity and clinical acceptability. The main types of recognition systems used in contemporary analytical instruments include enzymatic, immunological, aptamer-based, CRISPR-driven, and molecularly imprinted polymer (MIP) biosensors, each with unique benefits in terms of stability, sensitivity, and specificity. Enzymatic biosensors take use of the exceptional catalytic efficiency and selectivity of enzymes (kcat/K_m up to $10^2 \text{ M}^{-1}\text{s}^{-1}$), with the immobilization approach used having a significant impact on performance [106].

Long-term catalytic activity is maintained via entrapment in sol-gels, electropolymerized films, or PEG-based hydrogels; some systems maintain 80% glucose oxidase activity for 180 days [107, 108]. Thermostable enzyme variants with longer shelf lives engineered cytochrome P450s that can detect emerging contaminants like PFAS at sub- $\mu\text{g}/\text{L}$ levels, and multi-enzyme cascades that allow highly sensitive amplified detection, like lactate sensing down to 0.1 μM , are examples of recent protein engineering [109].

Nanoparticle-enhanced sandwich assays can now detect SARS-CoV-2 spike protein at 0.2 pg/mL in minutes [110] and cardiac troponin I at 0.05 ng/mL [111]. While label-free platforms using graphene FETs or impedimetric transduction offer quick PSA and multiplexed cytokine detection, competitive immunoassays allow the measurement of small molecules such as cortisol at 0.1 ng/mL [40] and aflatoxin B1 at 0.01 ng/mL [112]. With proven detection of CEA and CRP in therapeutically relevant samples, antibody substitutes such as scFvs and nanobodies enhance sensor stability, matrix penetration, and regeneration potential [113].

Aptasensors provide thermal stability, inexpensive manufacturing, and simple chemical modification. They are based on synthetic oligonucleotide aptamers that alter conformation upon interaction [114]. Applications like high-efficiency capture of circulating tumor cells from complex blood samples cocaine detection via gold nanoparticle aggregation, and MUC1 cancer biomarker detection at 0.1 nM using hybridization chain reaction amplification demonstrate their versatility [115].

By employing Cas12/Cas13 collateral cleavage to produce fluorescent or electrochemical signals, CRISPR-based biosensors provide programmable nucleic acid recognition with single-nucleotide precision [116]. Microfluidic CRISPR devices detect HPV DNA Atto molar levels [117], SHERLOCK accomplishes Atto molar viral RNA detection [118], and

DETECTR detects SARS-CoV-2 at 10 copies/ μL within 30 minutes without amplification [119]. DNA and mutations may be detected at femtomolar concentrations using new electrochemical techniques such as graphene FETs, impedance modulation, and ferrocene-reporter cleavage [120].

In large cohort testing, CRISPR-electrochemical sensors have demonstrated 97% sensitivity and 100% specificity for SARS-CoV-2. Lastly, strong, inexpensive synthetic receptors that can identify proteins, peptides, and tiny molecules even under challenging conditions are provided by molecularly imprinted polymers (MIPs) [56]. The sensitive detection of vancomycin at 0.5 ng/mL, bacterial toxins at 1 pg/mL, and steroid hormones like testosterone at 0.1 ng/mL in urine is made possible by advancements in surface and epitope imprinting, which have improved binding kinetics and selectivity [121, 122].

Together, these developments show how the field of biosensing is quickly changing due to tailored biorecognition components and hybrid materials that increase stability, push detection limits, and broaden practical applications.

Wearable and Point-of-Care Biosensors

Over the past five years, biosensing technologies for wearable and point-of-care (POC) applications have evolved quickly due to the requirement for decentralized diagnostics and continuous, real-time monitoring. Non-invasive biofluids (sweat, tears, saliva, interstitial fluid), miniature electrochemical transducers, multiplexed detection arrays, and long-lasting implanted sensors have all seen advancements. Better analytical performance, patient comfort, and clinical value are all provided by these improvements.

Wearable Biosensors for Continuous Monitoring

Wearable Biosensing devices can be used for a variety of body areas to monitor psychological and physiological indicators (in saliva, blood, urine, and sweat) that are critical for diagnosis and therapy [123]. For example, in diabetes, which is one of the underlying illnesses associated with an elevated risk of severe COVID-19 disease, continuous glucose monitor devices such as the Dexcom G6 are now commercially available, with a triple action: sensor, transmitter, and receiver. The automated applicator, the sensor wire is put beneath the skin, and the readings are relayed to the receiver and displayed in real time [62]. Another comparable technique aimed at diabetes monitoring and preventing problems is the creation of a tears-based wearable gadget, commercially accessible as Triggerfish [124], which monitors the intraocular pressure of glaucoma patients to diagnose diabetes. Challenges in monitoring cardiac patients may be addressed by developing a tattoo-based wearable device for ECG monitoring, which consists of miniaturized electronic components built on a graphene/PMMA bilayer substrate and is effective for monitoring various biopotentials such as ECG, EMG, and EEG signals [125, 126].

Patients with neurological conditions like epilepsy, Parkinson's disease, and Alzheimer's disease can receive feedback from wearables that are customized to an individual's physiological responses, such as heart rate, electrodermal activity—which is responsible for emotional status and skin temperature. These signals can be extracted using the autonomic nervous system [127]. Sweat-based biomarker monitoring that is suitable for everyday life and comes in a handy glove-based form for quick accumulation of natural thermoregulatory sweat without active sweat stimulation can be developed using another future technique to be sensing under routine and even inactive activities. Glove-based sensing platforms (nitrile gloves and finger cots) are appealing for in situ detection of various biomarkers, such as electrolytes and xenobiotics, because the fingertips, palm, and back of the hand have some of the highest sweat gland densities on the body and are accessible locations for monitoring natural sweat [128]. The development of contemporary wearable medical devices that can monitor vital parameters for the early detection of COVID-19, such as temperature, heart rate, sleep quality, and blood oxygenation, should be a major new driving force considering the new challenges associated with the COVID-19 pandemic.

Sweat-Based Sensors

Sweat's dense molecular composition has made it an essential biofluid for ongoing, non-invasive health monitoring. The development of wearable sweat sensors has advanced significantly in the last several years (2020–2025), overcoming previous obstacles related to stability, sensitivity, and sample collecting. For instance, continuous glucose detection in

sweat was shown via a flexible non-enzymatic electrochemical sensor utilizing a Pt/MXene ($\text{Ti}_3\text{C}_2\text{T}_x$) composite, exhibiting trends that closely mirror blood glucose dynamics under real-world settings [129]. Building on this, a Ga@MXene/chitosan hydrogel-based patch was created to optimize skin conductivity and conformity, obtaining a low detection limit of $0.77 \mu\text{M}$ and a wide dynamic range ($10\text{--}1000 \mu\text{M}$) appropriate for physiologically realistic sweat-glucose monitoring [130].

A Ti_3C_2 MXene/MWCNT (multiwall carbon nanotube) composite channel material is incorporated into a wearable bio-FET (field-effect transistor) drawn onto paper that provides real-time, multiplexed sensing of temperature, pH, and glucose with integrated calibration to account for sweat pH and thermal fluctuations [131]. Other approaches include the use of a three-phase solid-liquid-air interface for improved performance and lifespan, as well as modular biosensors based on MXene/Prussian blue ($\text{Ti}_3\text{C}_2\text{T}_x/\text{PB}$) composites that can be switched to detect either lactate or glucose [132].

For wearable biosensors, textile integration is still an appealing option. Lactate monitoring in sweat under strain has been made possible by stretchable gold-fiber electrodes woven into textiles, which preserve sensor sensitivity even at significant deformation [133]. In the meanwhile, non-invasive glucose sensing across a wide linear range ($0.04\text{--}3.08 \text{mM}$) with high stability and anti-interference capabilities was made possible by researchers' recent introduction of a $\text{Ti}_3\text{C}_2\text{T}_x$ MXene–polyaniline modified nylon fabric electrode [134].

Despite these significant developments, problems still exist. Accurate measurement is still hampered by variations in sweat composition, skin contamination, and sweat-rate variability. Additionally, long-term calibration and device drift continue to be major problems, particularly for continuous, practical usage.

Interstitial Fluid Sensors

Interstitial fluid ($50\text{--}1000 \mu\text{m}$) may be accessed minimally invasively using microneedle-based devices without triggering pain receptors [135]. Dissolving polymer microneedles for sensor deployment without disposing of sharps [136], 3D-printed patient-specific microneedles [137], and enzymatic microneedle arrays for continuous glucose monitoring with $\pm 10 \text{mg/dL}$ accuracy over 14 days are examples of innovations. Benefits of interstitial fluid monitoring include low latency for metabolic indicators, no clotting interference, painless sample, and direct access to extracellular proteins, antibodies, and cytokines.

Saliva and Tear-Based Sensors

Saliva and tear-based biosensors have developed effective non-invasive diagnostic tools because they include clinically relevant indicators that closely mirror systemic physiology. Saliva, which contains approximately 3000 proteins, metabolites, hormones, and antibodies, has been extensively studied for quick illness detection and point-of-care testing. Recent studies have demonstrated its strong diagnostic potential, with electrochemical assays detecting SARS-CoV-2 antibodies at 0.5ng/mL within 15 minutes [4] and therapeutic drug monitoring of anticonvulsants showing 92% concordance with serum levels [138], highlighting saliva's reliability as an alternative to blood sampling. Salivary inflammatory proteins including IL-6 and IL-8, which may be detected at quantities as low as 10pg/mL , have also been shown to be useful for early oral cancer detection [139]. Tear-based biosensing offers another inconspicuous platform, especially for chronic illness monitoring via wearable technology such as smart contact lenses. These devices can detect tear glucose in the $0.01\text{--}0.5 \text{mM}$ range utilizing flexible electrochemical interfaces [140], whilst sophisticated piezoelectric and pressure-sensitive designs can constantly measure intraocular pressure, assisting with glaucoma care [141]. These discoveries show how saliva and tear biosensors are developing toward real-time, painless, and patient-friendly diagnostics that may be widely adopted in clinical settings.

Despite these developments, wearable tears and saliva biosensors still face difficulties with calibration, individual variability, and guarantee long-term biocompatibility.

Point-of-Care Testing Devices

Although significant progress has been made in the development of nano-biosensors for point-of-care diagnostics such as cancer, diabetes, malaria, and HIV, it would be beneficial to investigate a broader category of nanomaterials with superior properties to improve sensor performance for larger applications. The incorporation of nanomaterials into point-of-care

testing, as well as the possibility of developing portable, user-friendly, cost-effective, and miniaturized analytical instruments, are ongoing challenges, particularly in personalized medicine. The next generation of point-of-care devices must overcome the current limitations of low detection sensitivity to distinguish biomarkers at various stages of disease, while improving molecular selectivity for monitoring patient health anywhere and at any time [142].

3D-printed microfluidic devices are one of the most promising methods. Researchers have created integrated microfluidic electrochemical devices that can automatically separate plasma from whole blood and identify biomarkers in a single step because additive manufacturing enables quick prototyping [143, 144]. For instance, a paper-based origami microfluidic device that combines mobility and high sensitivity has been shown to include cardiac protein indicators like troponin [145].

PADs, or paper-based analytical devices, are still essential to many POC platforms. For the simultaneous detection of many analytes, modern designs use multiplexed electrochemical electrodes that are printed directly on paper (Frontiers in Oncology, 2023). As evidence of the growing usage of paper biosensors in clinical diagnostics, these devices have shown picogram-per-milliliter detection for cancer biomarkers [146]. Potentiometric PADs for cardiovascular biomarkers, including myoglobin, have been developed concurrently, enabling reliable and quick disease screening [147]. Additionally, multiplexing is being scaled up: sophisticated ePAD (electrochemical PAD) devices now include numerous functional electrodes that may simultaneously detect inflammatory indicators, cardiac biomarkers, and more [147]. Conductive carbon nanoparticles are added to these devices to increase sensitivity and lower cost.

Recent aptasensor-based electrochemical POC devices provide quick detection of acute myocardial infarction biomarkers such as troponin I at the molecular recognition level. Real-time, decentralized cardiovascular diagnostics were made possible by a 2025 aptasensor study that showed high-affinity aptamers could accurately detect cardiac troponins in portable forms. Even while these POC devices are getting more affordable and sensitive, there are still a lot of obstacles to overcome. For wider implementation, it is still essential to guarantee long-term stability, reduce signal drift, and validate these sensors in actual clinical settings.

Implantable Biosensors

The development of implantable continuous glucose monitors (CGMs) has pushed the boundaries of biocompatibility and durability. Conventional CGMs, like the Ever sense line, sample interstitial fluid using subcutaneous electrodes that contain glucose oxidase. For instance, the Ever sense 365, with its fluorescence sensing chemical, has shown a year-long lifespan in clinical usage. These devices can stay implanted for months. Even long-wear sensors, however, encounter biological difficulties: fibrosis and foreign-body encapsulation can eventually degrade performance, and researchers stress the need for improved materials to increase long-term stability [148].

Optical insertable CGMs are now being developed to get around some of these restrictions. To infer glucose levels through the skin with high robustness against misalignment, a novel study published in 2024 described a phosphorescence-lifetime sensor embedded in a biocompatible hydrogel, coupled with a wearable reader and neural-network processing [149]. Compared to electrochemical sensors, this concept offers cheaper cost, less biological interference, and longer implantation periods. Simultaneously, biodegradable implanted biosensors are becoming more popular. To minimize long-term foreign-body responses and do away with the requirement for surgical removal, these sensors employ resorbable materials that progressively disintegrate [150]. In the future, these systems may offer short-term monitoring following surgery or in emergency situations without requiring long-term implantation.

However, challenges still exist. Problems including drift, immunological reaction, and reliable calibration under physiological settings continue even with optical or biodegradable systems. Designers must balance biological and engineering trade-offs to create true next-generation CGMs that combine long-term accuracy, low invasiveness, and patient-friendly operation for practical diabetes treatment.

Case Investigation and Medicinal Applications

According to estimation of World Health Organization, the infectious diseases continue to be a major source of illness and death worldwide, causing about 15 million fatalities each year (World Health Organization). The development of pathogens, resistive nature of microbes and possibility of pandemic occurrences, need rapid, precise and easily available technologies for diagnosis. Biosensors provide a groundbreaking development in diagnosis of infectious disease by providing quick, sensitive, and affordable detection techniques that close the gap between lab-based tests and clinical applications[151]. These analytical tools combine physical and chemical transducers and biological detection components to accurately identify certain infections, antibodies, or illness biomarkers. The incorporation of biosensing technology into clinical practice has changed the approaches of treatment, outbreak control, and monitoring[152].

Diagnosis of Infectious Diseases

Biosensors for Corona

The pandemic of COVID-19 served as an example of importance of biosensors to control the infectious diseases. Despite its great accuracy, traditional RT-PCR testing had drawbacks in terms of accessibility and response time. Field-effect transistor (FET) biosensors loaded with SARS-CoV-2 spike protein antibodies showed quick and highly specific detection of virus in samples collected in nasopharyngeal cavity in time duration of fewer minutes[153]. Extensive community screening was made possible by the Abbott ID NOW system which is a handheld isothermal nucleic acid amplification-based biosensor that produced outcomes within 13 minutes [154]. SARS-CoV-2 spike protein was found in saliva and detected at concentration of 0.2 pg/ml by the magnetic bead-based sandwich test in just 15 minutes [110]. An electrochemical device based on paper identified IgM/IgG antibodies around 0.5 ng/mL, differentiating between severe and recuperating infections [4]. Graphene FET based biosensors detected COVID-19 from swabs of patients' nasal cavity with sensitivity of 97% and a specificity of 100% [155]. Electrochemical biosensors that use CRISPR-Cas systems have become revolutionary tools for diagnosis with detection limits in comparison to PCR in 30 to 45 minutes [156]. In 30 minutes, SHERLOCK detected 10 copies of virus in 1 μ l with no amplification by combining Cas13 with electrochemical output [118] Wastewater monitoring with CRISPR-based biosensors identified illnesses of community five to seven days prior to clinical infections [157].

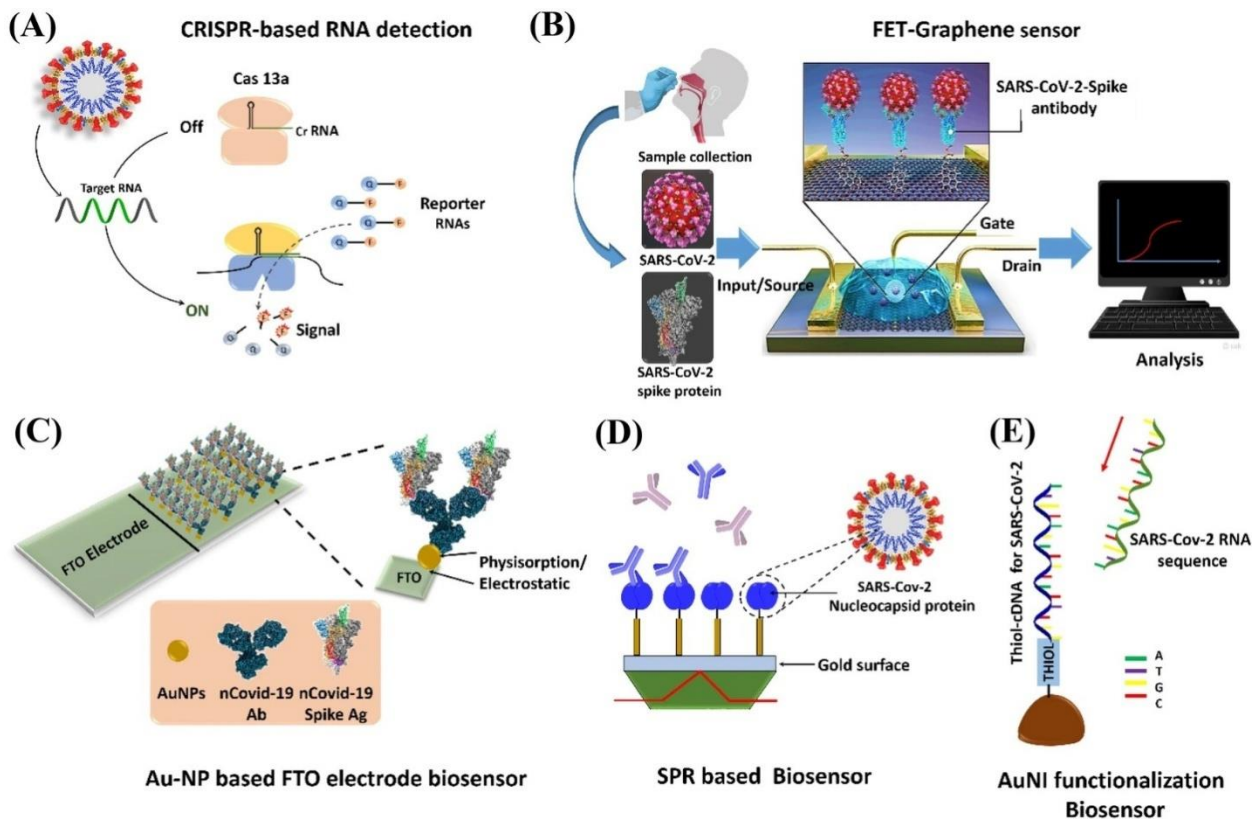


Figure 5: SARS-CoV-2 biosensing with A) CRISPR Cas system B) Biosensors based on Graphene FET C) Gold nanoparticles fabricated on FTO electrode as biosensors D) Surface Plasmon Resonance (SPR) based biosensor E) Two dimensional Au-nano films as functionalized biosensors [158].

These developments greatly impacted pandemic prevention strategies globally by facilitating early identification of case, contact tracking, and infection control procedures. The development of biosensors was also accelerated by this pandemic from laboratory research to deployment in clinics within one year [159].

Biosensors for Bacterial Infections

Diagnosis for infections caused by various bacteria have been improved by biosensors bacterial especially to address the drug resistance. Impedimetric biosensors identify bacterial metabolism and tolerance patterns with monitoring shifts in electrical impedance while bacteria proliferate in an environment full of antibiotics shortening detection [160]. *Enterobacteriaceae* (resistive to Carbapenem) and *Staphylococcus aureus* (resistive to Methicillin) can be directly detected from cultures of blood using aptamer-based biosensors with remarkable specificity [161]. In patients with HIV, electrochemical identification of lipoarabinomannan (cause tuberculosis *Mycobacterium tuberculosis*) in urine attained sensitivity about 85% and filled the significant gap in diagnosis [162]. By lowering unnecessary use of antibiotics and preventing the development of bacterial resistance, these sensing technologies enable tailored antimicrobial therapy.

Biosensors for Viral Infection beyond COVID – 19

Applications for biosensors cover a wide range of viral infections. Testing at the point of care for HIV, influenza, hepatitis B and C and dengue viruses have been revolutionized using lateral flow immunoassay biosensors [163]. Preliminary infection detection before symptoms appear is made possible by electrochemical DNA-biosensors that use carbon nanotubes and nanoparticles of gold to detect virus nucleic acids with femtomolar sensitivity [164].

Significant progress has been made in the past few decades in creating biosensors for a number of important medical viruses [165].

Biosensor for Fungal and Parasitic Infections

Fungal infections have a significant impact on global health and need a significant number of resources for treatment. Since a delayed identification of a systemic infection nearly invariably results in a bad prognosis, prompt detection is essential to the effective treatment of fatal infections that originated from fungal pathogens and parasites. Multiplex cytokine biosensors (IL-6, IL-8, and procalcitonin) identified septic shock four hours ahead of clinical measures with about 93% precision [166].

The emergence of infection by parasites could be significantly controlled by electrochemical biosensors. In endemic areas, lactate dehydrogenase biosensors allowed remote diagnosis by detecting 5 parasites per microliter in just 20 minutes (Ahmed et al., 2021). Monitoring systems of public health, assessment of treatment, and control of transmission of infectious diseases are all aided by biosensors.

Diagnosis of Cancer

By offering quick, sensitive, and less invasive methods for detection and observation of illness the invention of biosensors has fundamentally altered the field of clinical diagnostics.

Biopsy

Cancer diagnosis has been changed significantly by the development of liquid biopsy technologies, which enable monitoring of non-intrusive disease by utilizing blood-associated biological markers. One of most effective of these is Circulating tumor DNA (ctDNA) testing. CRISPR electrochemical sensing can identify the single-nucleotide variations with frequencies of alleles as small as 0.01%, allowing for extremely sensitive tracking of little residual illness following treatment [167]. This sensitivity enables professionals to detect tumor recurrences several weeks or months sooner compared to standard imaging, enabling more prompt treatment.

Additionally, exosome-driven diagnosis has developed quickly. Cancer-derived exosomes are captured by impedimetric biosensors engineered with CD63 and EpCAM antibodies. The detected amount was 104 particles per microliter with an accuracy of 92% in differentiating people with cancer from individuals in good health [168]. Exosomes provide a complete picture of the state of the illness from a simple specimen of blood since they contain both proteomics and genetic fingerprints of malignancy.

Protein Biomarkers

Clinically innovative detection limits have been attained through individual biomarker-dependent sensors. The CA-125 sensors have ability to detect the minimum amount (0.001 U per milliliter) initial-staged ovarian cancer [169]. 0.1 pg/ml can be detected by PSA biosensors [170]. These developments help precision oncology, which bases therapy decisions on actual molecular data rather than empirical methods. Simultaneous measurements of 10 cancer biomarkers like HER2, NSE, CA 29-9, CEA, ProGRP, in 10 microliter serum have been reported by use of multiplexed electrochemical arrays [171].

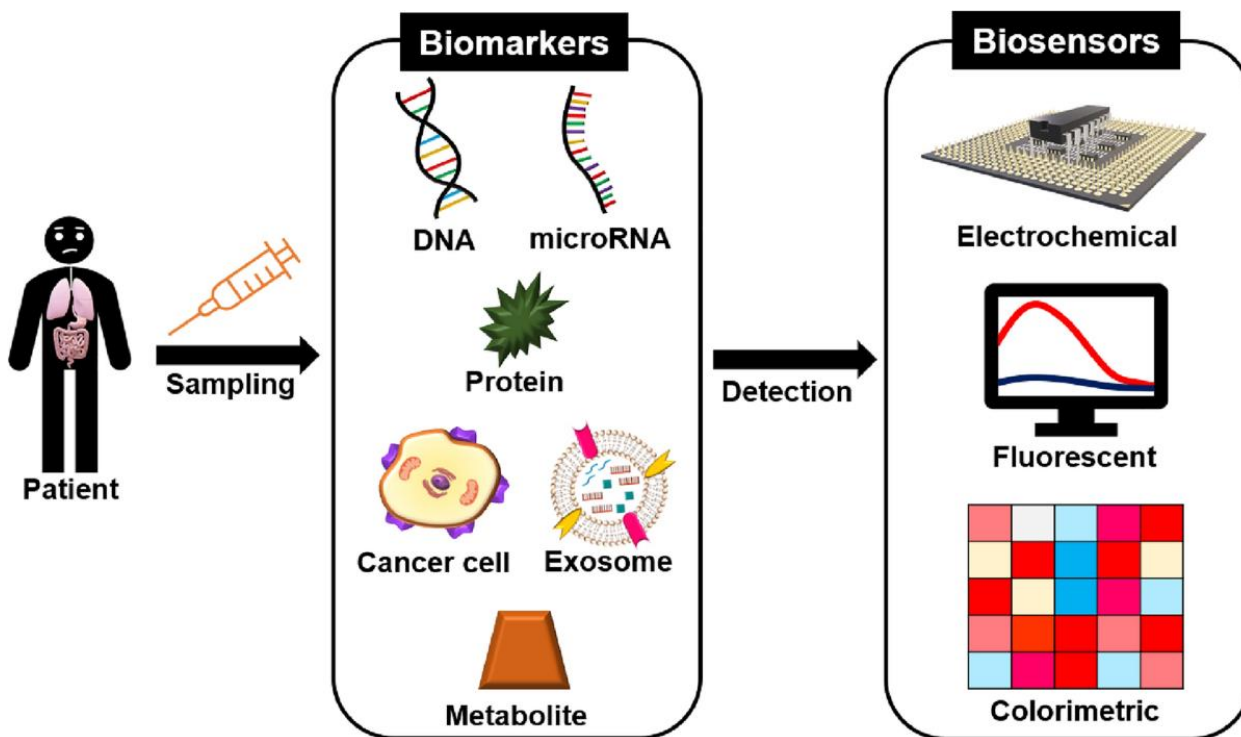


Figure 6: Detection of Cancer Biomarkers by various Biosensors[172].

Additionally, these sensing technologies are especially useful for pediatric cancer patients and resource-constrained settings where blood volume limitations and laboratory infrastructure pose major hurdles due to the small sample quantities needed and quick reaction times [113]. Early cancer detection using biosensor monitoring provides economic benefits as these greatly enhance the results of treatment while lowering the medical expenses linked to management of advanced illness.

Diagnosis of Cardiovascular Diseases

The cardiovascular arrest has been the top reason of death worldwide. The cardiac biosignatures need to be accurately and rapidly detected for quick assessment and longstanding risk categorization.

Detection of Troponins:

Troponins are released in blood when a person has cardiac disorder. Graphene based biosensors have detected the myocardial problems by highly sensitive troponin tests with 0.5 pg in one milliliter, attaining minimal detection limit in just 10 minutes. This makes the cardiac diagnosis must faster system than the traditional ones [173].The development of nanozyme driven ELISA examinations have detected troponin in very small amount of 0.05 ng/ml straightforwardly in the blood without need of any complex lab-based setups, making them usable in bedside manners [174].Scientific studies have revealed the 98% accuracy in detection of these advanced biosensors to identify and track the cardiac attack within earlier of symptoms appearance [175].

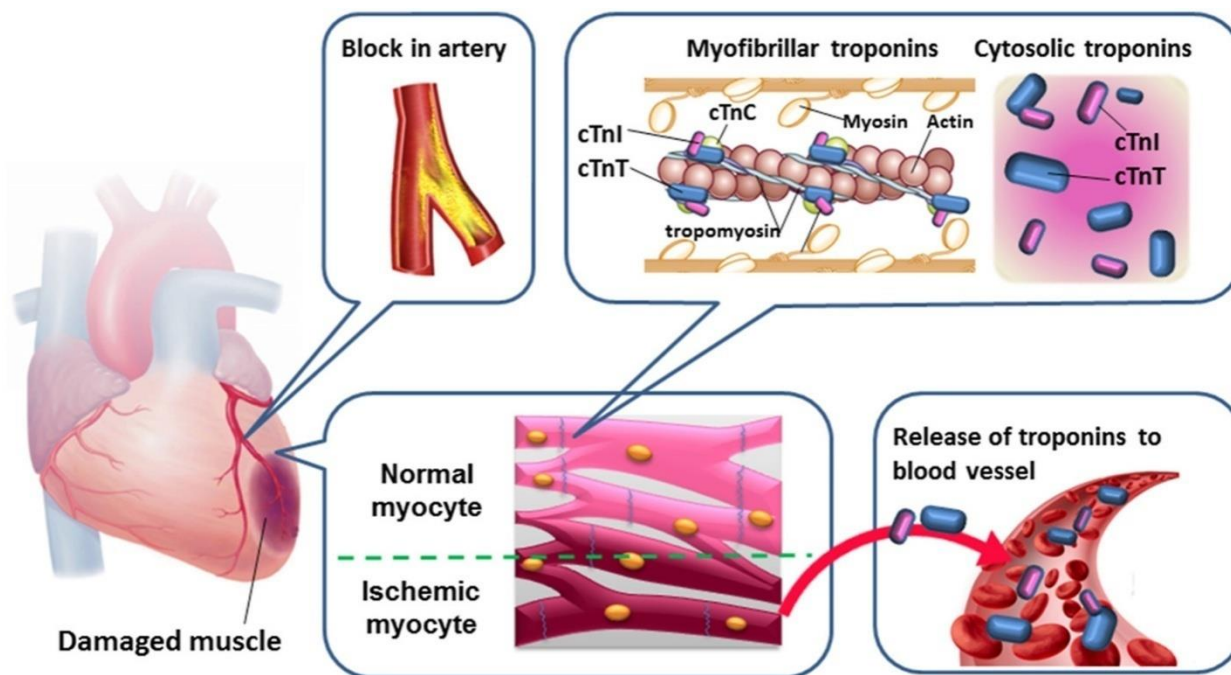


Figure 6: Detection of cardiac troponin in acute cardiac disease by using voltametric biosensors [176].

B-type Natriuretic Peptide (BNP) Testing

BNP is a hormone whose level in blood describes the health-conditions of heart. BNP-biosensors have helped doctors to monitor heart failure. These advanced biosensors are so sensitive that these can detect the BNP in very small amounts (1 pg in one milliliter), enabling patients to monitor their heart health even at home and catch any worsening condition of heart before appearance of symptoms[40].

Biosensing of cardiovascular conditions does not only help in case of emergency but also provide support for long-term care. Biosensors which are capable of being implanted can track the changes in body with time and provide person's response to diet, medicines, making personalized treatment possible [113]. Multiplex biosensor can detect many markers at one time which provide collective pictures of any risk factor. Jo et al reported the combined detection of BNP and CRP protein to predict heart condition [40]. Such advanced biosensing tools shifted the heart care from emergency treatment to proactive monitoring [174].

Management of Metabolic Diseases

The way of managing metabolic disorders has been altered due to development of biosensors. Rapid and significant decisions about health of people could be made by monitoring chemicals released in body through biosensors which gave actual information about these chemicals.

Diabetes

The Continuous Glucose Monitors (CGMs) have revolutionized the treatment and management of diabetes by providing measurements of glucose at regular intervals rather than testing finger-prick testing, Clinical trials often demonstrate significant advances in managing blood sugar when CGMs are combined with automatic delivery of insulin or artificial intelligence-powered prediction systems. In the recent reported work, artificial intelligence-based closed-loop insulin devices boost times-in-range (TIR) and decrease the duration of hypoglycemia and hyperglycemia in patients in comparison to standard treatment or sensor-controlled pumps [177]. Similar improvements in average stability of glucose

and significant decreases in hypoglycemia-related events have been shown by closed-loop "artificial pancreas" methods, which integrate CGMs with programmable insulin pumps and continuously monitored algorithms [178]. Additionally, hypoglycemia can be predicted ahead of time by machine-learning models connected with CGM systems, enabling preventive therapy. Deep transfer learning was used in a single investigation to anticipate low-glucose occurrences in individuals with type 2 diabetes with great precision [179]. Figure 7 unambiguously shows that continuous technology of biosensors results in quantifiable and clinically substantial improvements over many metabolic and athletic applications.

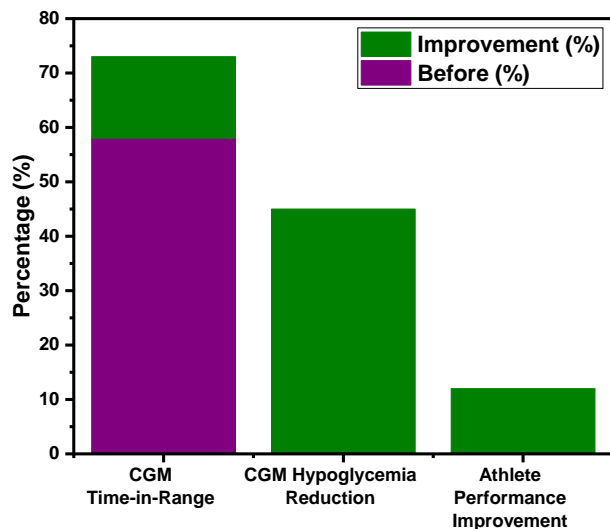


Figure 7: Impact of biosensing technologies on Metabolic Management.

Phenylketonuria (PKU)

Phenylketonuria is a genetic disorder in which person should prevent the high intake of phenylalanine in his food. Time-taking regular testing of blood makes the patient uncomfortable. Instant measurement of phenylalanine by using wearable biosensors helps in maintaining the diet and daily routine which reduces the hazard of neurological issues [179]. This technology specially helps the PKU in children because it eliminates the strict diet schedule for them [138].

Training of athletes:

The patches for lactate sensing for athletes give actual information in case of muscle fatigue. It has been reported that those athletes who use these biosensors improved their activity by about 12%. In this way they can easily be trained with accuracy.

Future gadgets will simultaneously track several substances, including ketones, glucose and lactate etc. These integrated streams of information can identify early indicators of metabolic issues years prior to symptoms manifest [180]. These advances will transition from sports and particular clinics into general healthcare with more affordable technology, enabling health to be much simpler for everyone to control.

Biosensors in Food Protection and Environmental Surveillance

Biosensing beyond Clinical Medicine

Biosensor applications are typically related to medical diagnosis, most notably monitoring blood sugar levels, detection of infectious illness, and assessment of biomarkers. However, during the previous decade, the utilization of their space has

increased dramatically, fulfilling significant requirements in food hygiene, environmental tracking, and healthcare management [181, 182]. As worldwide supply chains become more complicated, the dangers of contamination by microbes, falsification by chemicals, and allergenic interactions have magnified, needing quick, portable, and extremely sensitive diagnostic methods [182].

Despite the high accuracy and authenticity, the traditional techniques like chromatography, chromatography, cell-based assays and mass spectrometry have significant disadvantages owing to their lengthy processing period, the need for highly qualified staff, and a reliance on complex laboratory equipment [183]. These restrictions result in delayed epidemic detection for pathogens found in food, which causes epidemics and expensive recalls. When contaminants like organic substances or heavy metals are not promptly detected, damage to the environment can continue unchecked. Biosensing technology has overcome many challenges in food management by providing actual, on-spot and fast detection method for chemicals and biological risks[184].

Detection of Pathogen in foodby Biosensors

Pathogen generated in food like *Escherichia coli*, *Campylobacter jejuni* and *Listeria monocytogenes* are main cause of morbidity globally. The long-time conventional cell-based detection cannot provide timely treatment in food processing and distribution methods. On the other hand, biosensors enable early monitoring and detection at critical criteria of control process and anticipatory management of contaminants.

Detection of Bacteria-based pathogens

Electrochemical platforms

These types of biosensors are one of top reported sensors for the detection of microbes owing to their cost-effective, highly sensitive and compatible miniaturization approaches Zhou et al, reported modification of electrode with bacteriophage which showed impressive success in detection of *E. coli* O157:H7 with 11.3 CFU/ml in 30 minutes., better than the culture based approach [185]. Moreover, biosensors consisted of bacteriophages fabricated on active cellulosed matrix, demonstrated the extra sensitive detection at 3 CFU/ml[186]. Such sensing frameworks offer recognition of hosts owing to high specificity and preserve performance in complicated matrices of food.

Similarly, detection of *Salmonella* has been advanced by combination of magnetic bead capturing and electrochemical data, attaining 10^2 CFU/mL limits[186]. Reduction of Matrix intervention and more concentration of target cells have been improved through magnetic beads.

Surface plasmon Resonance (SPR) and Optical Biosensors

Immunosensors based on optical fibers have been investigated for detection of *Listeria monocytogenes* with 10^1 CFU/milliliter detection limits. Similarly, has been successfully sensed in poultry products by SPR-sensors with outstanding activity[184, 185].

Detection of Non-Culturable Pathogens

Viable and non-culturable microbes are commonly found in processed food. These have ability to escape basic culturing and keep virulency which causes unknown hazards. Biosensors can recognize these microbes [183].

Multiplexed Monitoring of Pathogens

Recently, Multiple pathogens can be detected by simultaneously via biosensing technology through collections of restrained identification elements. This ability of biosensors significantly increases the efficacy of detection in food managing resources where contamination by multi-pathogen frequently occurred. Nevertheless, there are few challenges

related to authentication within foods having variable pH, viscous medium, fat amount, and microbic conditions, which require optimization of specific matrixes [185].

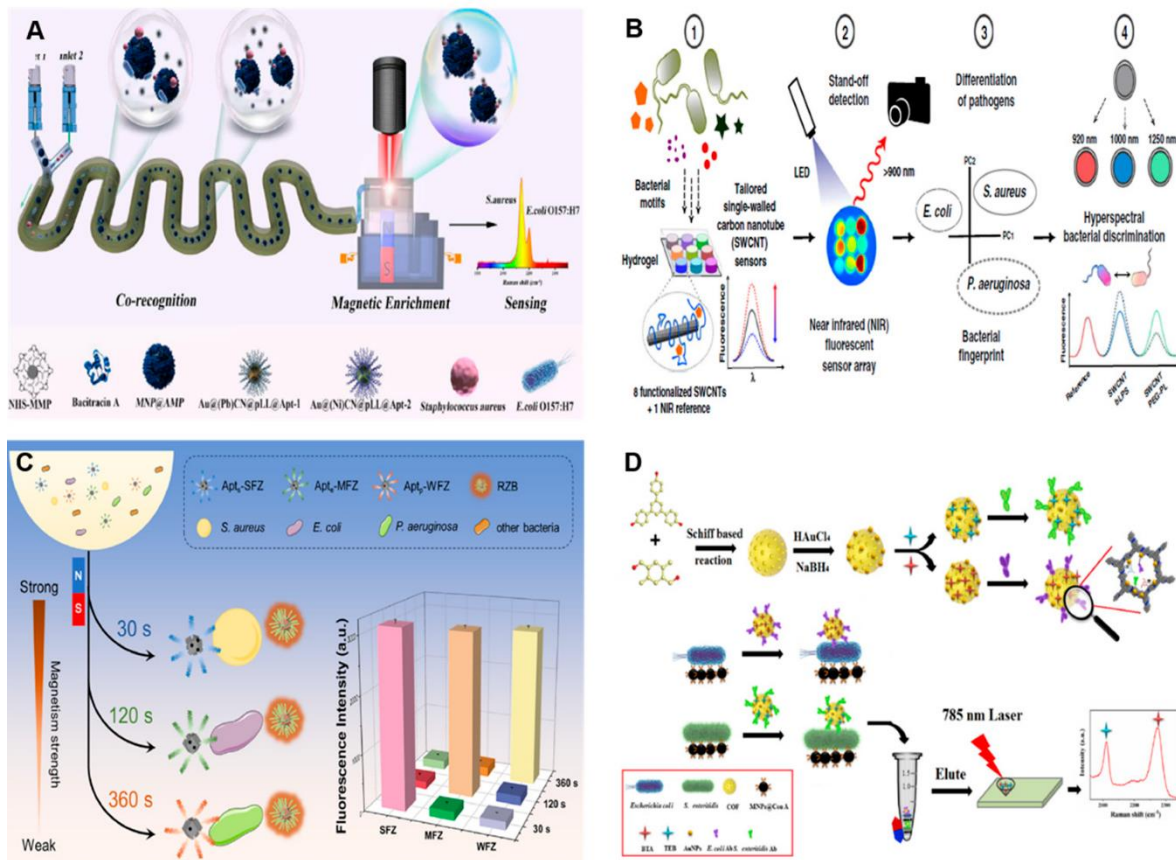


Figure 8: Multiplexing of multi-microbial detection of Nanomaterial based optical biosensors [187].

Detection of chemical contaminants

Screening of Pesticidal Residues

Organophosphates based on pesticidal residues cause chronic problems like cancer, neurotoxicity and endocrinal disorders. Biosensors based on Acetylcholinesterase are strong devices for the detection of organophosphates for example, methyl parathion and chlorpyrifos retarded the regulatory limits in lower concentration of 0.1 parts per billion [184, 188]. The conversion of irretrievable inhibition process into detectable biochemical indicators is remarkable achievement of biosensors. Glove-integrated biosensors provide feasibility to formers and workers on field to identify dangerous levels of exposure within few minutes [189].

Monitory of Heavy Metals

The accumulation of heavy metal such as cadmium, arsenic, lead and mercury in food chains, particularly aqueous medium, can be identified with the help of biosensors. The bacterial, enzymatic and DNA probes integrated in biosensors provide the best level of detection even in very low concentration for example, Lead (Pb), mercury (Hg) and cadmium (Cd) have been detected in 0.1, 0.5 and 0.5 parts per billion respectively [190-192]. One of the advantages of using such biosensors is their cost-effectiveness in low resource areas, compared to other conventional detections methods,

Detection of allergic components in Food

In vulnerable people, even the trace amount of allergen could be fatal. The advancement in biosensing can detect presence of allergic factors in food. Allergen like Peanut, lactoglobulin in milk, and gluten have been reported with detection limit of 0.1, 0.5 and 1 parts per million [193, 194].

Application for Environmental Monitoring

Assessment of Water Quality

There is need for systematic monitoring of water pollutants like heavy metals, organic compounds and microbes. Multiplexity of biosensors are very helpful in recognition of different contaminants simultaneously which enable the actual decision for authorities of water supply. This technology are helpful in rural areas without any laboratory testing [195].

Investigation of Biochemical Oxygen Demand

The optimization of wastewater treatment in real conditions needs a compatible system for BOD testing. The limit of detection has been reduced to 15 minutes through utilization of bacterial biosensors for oxygen consumption by water based restrained microorganisms [196].

Monitoring of aerosols and quality of Air

Microbial base whole cells Phage-based biosensors can detect the pathogen in air which affects the quality of air and cause various airborne diseases with the prior alarming systems for biological defense, work-related safety, and hospital contamination control [196]

In short, Biosensors have substantial assurance for converting food protection and environmental examining with regular advancement in designing next-generation anti-fouling substances, standardizing the authenticity protocols, AI-driven monitoring and IoT sensors integration.

Challenges in Biosensor Technology

In the last few decades, scientists have developed thousands of advanced biosensors, yet fewer than 5% of them are used in hospitals or are commercialized. This significant gap between laboratory research and practical application is sometimes referred to as the "valley of death." Scientists at universities mostly work on developing more inventive or sensitive biosensors. However, businesses want devices that are stable, dependable, repeatable, reasonably priced, and simple to obtain regulatory approval [197]. Many biosensors function flawlessly in the lab but fail when tested with actual blood, environmental samples, or by regular users due to their increasing complexity with nanomaterials and sophisticated signal systems [154].

Biofouling and Poor Performance in Real Conditions

Biofouling, which occurs when proteins and other molecules from samples like blood adhere to the sensor surface, is one of the main challenges. This reduces performance by 50 - 90% in a matter of hours by preventing the target analyte from getting to the sensor [198]. Fouling is nearly inevitable due to the thousands of proteins found in blood, including albumin, which is present at 35 - 50 mg/mL. Researchers have created anti-fouling coatings such as PEG-coated surfaces that retain 85% sensitivity for two weeks [199] and zwitterionic polymers that minimize undesired protein adhering by 95% in long-term testing. To free bound proteins, certain novel surfaces can even electronically alter form [200]. By obstructing big molecules, membranes like Nafion also aid [198].

All these alternatives, though, have drawbacks. According to Wisniewski and Reichert (2000), coatings reduce sensor sensitivity by 20 - 40% [201]. Because cells like red blood cells and platelets generate more severe fouling, many coatings fail in whole blood [202].

Problem of Similar Molecules

Biosensors need to differentiate the target analyte from several molecules that are identical. Because interferents like ascorbic acid, uric acid, and medications like acetaminophen create signals at comparable voltages, electrochemical sensors particularly suffer. For instance, ascorbic acid may readily mask neurotransmitter signals since it is present at concentrations 10–100 times greater than those of neurotransmitters [203]. Researchers employ methods such as selecting certain voltages, including charge-selective membranes, or employing sophisticated methods that separate overlapping signals, such as DPV and SWV [202]. Another level of selectivity is added by biological recognition components such as aptamers and antibodies [154]. Additionally, matrix effects in complicated data may be corrected via machine learning [204].

Lack of Standards and Regulatory Barriers

The lack of accurate, acceptable guidelines for biosensor testing is another significant problem. Different methods of calculating detection limits, such as 3σ , 10σ , or signal-to-noise ratios, are used by researchers, which results in conflicting findings among investigations [205]. Additionally, sample types and stability tests differ greatly [202]. Because minor changes in nanoparticle size or surface chemistry can vary performance by 20–40%, nanomaterial-based sensors have even more repeatability issue [154]. Despite efforts by organizations like ISO and IUPAC to give norms, acceptance is still lacking [206]. Regulatory approval is costly and time-consuming, particularly when it comes from the FDA. Class III devices may cost \$2–10 million and need clinical trials, whereas Class II devices typically require \$500,000–2 million and 1–2 years for approval [197]. Academic startups frequently lack the resources to meet these demands.

According to Thévenot et al. (2001), analytical validation requirements include linearity throughout the physiological or clinically relevant concentration range, precision assessment with coefficient of variation (CV) below 5%, accuracy with bias under 5% in comparison to reference methods, and sensitivity meeting clinical decision thresholds [205]. Clinical validation requires a minimum of 100–300 clinical samples obtained from different regions that represent the target illness frequency and demographic diversity, with sensitivity and specificity surpassing 95% when compared to recognized reference techniques [206]. According to device claims, stability testing must show a shelf-life of more than 12 months under defined storage circumstances and operational stability for 7–14 days of continuous or recurrent usage [154]. Safety testing covers electrical safety for powered devices, biocompatibility in accordance with ISO 10993 standards for materials contacting blood or tissue, and increasingly, cybersecurity for networked biosensors susceptible to hacking that could change glucose readings or insulin delivery [202].

Table 6: FDA Device Classification and Regulatory Requirements for Biosensors

Class	Risk Level	Regulatory Pathway	Timeline	Cost Estimation	Examples
I	Low	510(k) exempt	3-6 months	\$100K-500K	Glucose test strips (OTC)
II	Moderate	510(k) clearance	1-2 years	\$500K-2M	POC cardiac troponin, CGM accessories
III	High	Pre-Market Approval (PMA)	2-5 years	\$2M-10M	Implantable glucose sensors, novel biomarkers

Significant obstacles are presented by the expense and duration of regulatory approval, especially for small businesses and university spinoffs with limited financial resources and regulatory experience (Table 6). For Class II devices, basic 510(k) submissions cost between \$500,000 and \$2 million over a period of one to two years, but PMA applications for Class III devices cost between \$2 and \$10 million over a period of two to five years, with only 60–70% of first-time submissions being successful [197]. Large, well-established medical device firms have financial obstacles that disadvantage creative startups since these significant expenditures must be made before any income is generated. Following high-profile device malfunctions and cybersecurity issues, the regulatory burden has grown in recent years. FDA examination has been more intense, especially for artificial intelligence-enabled diagnostics and continuous monitoring systems.

Manufacturing Challenges: Scaling From Lab to Industry

Large-scale production of a biosensor creates new issues, even if it operates in the lab. Nanomaterials exhibit batch-to-batch variability of 10–30% [204]. When immobilized on electrodes, enzyme activity decreases by 30–60% [198]. To provide repeatable outcomes, screen printing and inkjet printing require incredibly strict supervision [202].

Economic Challenges and Business Models

It usually takes 6–12 years and \$10–70 million to develop a biosensor from concept to commercialization [197]. Additionally, market pricing is competitive; many tests must be priced between \$1 and \$50. The razor-blade model (cheap reader, costly disposable strips), service-based models for hospitals, and data subscription models for wearable sensors are demonstrations of successful approaches [206].

Although biosensors offer a lot of assurance, there are a lot of obstacles to overcome, such as biofouling, selectivity problems, a lack of standards, regulatory obstacles, manufacturing difficulties, and financial pressures. Researchers, business, regulators, and healthcare practitioners must work together to find solutions to these problems.

Future Perspectives and Emerging Trends in Biosensor Technology

Advances in nanotechnology, artificial intelligence, biotechnology, and sustainable materials are propelling biosensor technology toward a revolutionary phase. Commercial gadgets like cardiac biomarker testing and continuous glucose monitoring have shown promise, but they are simply the start of a transition toward autonomous, multimodal, AI-enhanced, and ecologically conscious systems. More dependable, ongoing, and customized monitoring is promised by these new systems [207]. Battery reliance is a significant drawback of existing biosensors, limiting their long-term usage. Self-powered systems use the body's or the environment's energy to handle this. Endogenous metabolites like glucose or lactate can be transformed into useable energy by biofuel cells [208]; lactate-based devices work effectively during times of high metabolic activity. Although storage components are still needed, textile-integrated designs show promising output for low-power sensing [209]. Triboelectric nanogenerators create electricity from movement. Self-calibration algorithms and low-power communication like NFC backscatter provide further assistance for autonomous operation [208].

According to Zhang, Korolj, and Radisi multimodal sensors that include electrochemical, optical, piezoelectric, or thermal methods increase specificity and decrease sensor drift [210]. Cross-validation of data and more dependable analysis are made possible by hybrid formats, such as electrochemical–optical or piezoelectric–electrochemical systems [135]. Robustness is further improved by data fusion techniques such as Bayesian inference [211]. Biosensing platforms that are physiologically relevant are being created through organ-on-chip integration. These micro physiological devices enhance drug testing and illness modeling by incorporating sensors for metabolites, oxygen, pH, and cytokines [212, 213]. For example, tumor-on-chip devices that monitor lactate generation aid in the characterization of cancer metabolism [210]. Biosensor capabilities are being quickly advanced by AI. By demonstrating how predictions are formed, explainable AI fosters trust [213]. While causal inference and generative AI facilitate individualized decision-making and expedited material discovery, federated learning allows for large-scale model improvements without data sharing [211].

By enabling real-time monitoring of medication levels, metabolites, and inflammatory indicators to improve treatment and identify early illness changes, these developments support the objectives of personalized medicine [213]. Additionally, disease subgroups, like those in type 2 diabetes, may be refined with multimarket monitoring [211]. Electronic waste can be decreased by using sustainable biosensors composed of biodegradable materials such as cellulose, silk fibroin, zinc, and magnesium. Environmental responsibility is further supported by green nanomaterial manufacturing and recycling techniques [214]. Achieving stable energy harvesting, validating organ-on-a-chip platforms, enhancing the stability of biodegradable materials, and updating regulatory frameworks are still technical problems [213].

However, a new generation of autonomous, accurate, and environmentally friendly biosensing is being made possible by the convergence of self-powered systems, multimodal sensing, artificial intelligence, organ-on-a-chip models, and sustainable materials.

CONCLUSION

Biosensor technology has appeared as a transformatory force in advanced diagnosis, primarily reforming the detection of illness, monitoring of health, safety of food security and protection of environment. This inclusive review has provided a detailed spectrum of applications of biosensors from well-known clinical diagnosis comprising regular glucose detection, investigation of cardiac biomarkers to developing borderlines in cancer biopsy, examination of pathogen in food pathogen and monitoring of environment. The systematic abilities depicted that these fields are outstanding: CRISPR-integrated sensors for detection of DNA of tumor in blood at allele frequency of 0.01%, electrochemical techniques for identification of foodborne microbes at detection limits of 10 CFU/ml in less than 30 minutes, and multiplexed arrangements which measure more than ten biomarkers of cancers simultaneously in 10 microliter serum with precision of 89%.

Nonetheless, despite the decade of research work on biosensing, the step towards shifting from lab-based prototyping to commercialized products is still a trouble having extensive obstacles that have restricted wide applicability. Accuracy is compromised by challenges like Biofouling which reduce 50% to 90% of the sensitivity in bio-matrices, false signals generation by electrochemical interfering factors owing to selectivity issues and effect of matrices in complicated systems. The tough economic obstacles are created by the lack of agreement criteria which builds reproducibility problems during governing authorization pathways and demands about 500,000 to 10 million dollars at the end of 2-5 years. Modern scale-up leads to about 10 – 30% changes in properties of nanostructures and loss of 40 – 70% enzymatic performance during the process of immobilization which is a challenging situation in transforming bench-scale manufacturing to commercial engineering.

The emerging solutions that deal with significant restrictions include 1) development of Zwitterion-based polymer layers which minimize the biofouling up to 95% for at least 30 days, 2) multi-platforms for biosensing deliver orthogonal proof and enhance accuracy, and 3) matrix variation is adjustable by integrating AI – based algorithms in multi-variate calibrations.

The upcoming of biosensor technology confirms groundbreaking advancement via convergence of numerous innovations. Battery limitations will be addressed by development of self-power-driven biosensors which could harvest energy from oxidation of glucose or body movement and provide complete autonomous strategies. Biosensors integrated with miniature organ models would transform the development of drugs and disease demonstration with physiological relevancy which are quite impossible with conventional methods. The tailored applications of medicine will be possible by advancement of Artificial intelligence from sample identification to fundamental interpretation and propagative schemes which speed up the development. The environmental conditions would be better addressed with the fabrication of sustainable biosensors using eco-friendly substances, for example silk fibroin-based substrates and magnesium-electrodes without compromising on analytical performance.

The definitive vision includes consistent, 1) self-directed monitoring of health which can detect diseases even at molecular steps when interference is dominant, 2) optimization of treatments according to profile of individuals, and 3) transition of health care from emergency treatment to prior prevention of disease. The upcoming decade will establish the applicability of biosensors in life saving and disease preventing strategies with precise diagnosis rather than publication-based research and will reach out to the entire populations of globe.

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