REVIEW ARTICLE

Nanotechnology enabled smart biosensors in monitoring and maintaining balanced health: A Review

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Abstract: The pandemic outbreaks such as severe acute respiratory syndrome, swine flu, Middle East respiratory syn-drome, Ebola, zika virus outbreak, and coronavirus are influential events that were transmitted through various countries in a short period. Due to sudden outbreaks of this pandemic and unavailability of rapid diagnostic kits, strategic management, and treatment caused a high rate of mortality and mortality. Primarily diagnosis and detection of infections are performed through tedious pathological tests; however, the recent advancements in nanotechnology-based robust sensors are handy and rapid to detect such infections. Smart biosensors offer promising prospects such as portability, flexibility, multifunctional use, and efficient operation that provides fast and real-time response against tested components. The biosensors act as an interface between biological analytes and quantifiable electrical signals. Enabling this biosensor with nanotechnology has not only revolutionized the diagnosis of infection but also regular health checkups. The present review presents compressive updates on different types of sensors available to measure health conditions, with elaboration enabling sensor processing using nanotechnology. Moreover, the safety consideration and applicability of wearable sensors in day-to-day routine activity.

Keywords: Sensors; Chemical sensor; Smart sensor; Nanotechnology; Nanomaterials; Smartwatch.

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1. INTRODUCTION

One of the most significant aspects of a person's life is their health however, many individuals have numerous limitations when receiving care because of the inadequate technology in healthcare facilities. Providing high-quality healthcare services requires prompt decision-making based on speedy diagnosis, sophisticated data analysis, and informatics. Nanotechnology has significantly benefitted the healthcare industry, some of which developments include sensitive diagnostic kits, biosensors, drug delivery systems, implants, and more (Jayeoye, Eze, Singh, *et al.*, 2021; Kumar *et al.*, 2024). These days, nanotechnology in biomedical has become important as it is required to provide medical help to people by monitoring, controlling, detecting, and acting based on the data, which reduces healthcare costs significantly (Verma *et al.*, 2022). Biosensors (BSs) are portable and cost-effective equipment that can instantly detect pathogens, proteins, and other analytes. These sensors aim to eliminate the need for specialist expertise and time-consuming testing processes, which may be costly in some sectors. The International Union of Pure and Applied Chemistry (IUPAC) defines "a biosensor as a device that uses specific power of the isolated enzymes, immune systems, tissues, organelles, and whole cells to detect chemical com-pounds by interpreting the signals like electric, thermal, and optical cues, triggered by specific biochemical reactions (Farré & Barceló, 2020). Transducers, nanotechnology, and signal amplification methods have all made significant advances in biosensors in recent years. Nanotechnology-enabled smart biosensors are used to detect and diagnose metabolites in the human body, also they provide targeted drug and gene delivery due to their ability to target specific areas. Nanoparticles (NPs), nanotubes, nanowires, and nanocomposites are all examples of nanostructure that may be employed to increase the efficiency of the sensors (Jayeoye, Eze, Olatunde, *et al.*, 2021; Jayeoye, Eze, Singh, *et al.*, 2021; Jayeoye *et al.*, 2024; Kumar *et al.*, 2023). Despite their fascinating features, these nano-biosensors have certain drawbacks, including drift, fouling, no specificity, and the presentation of irreproducible and non-uniform transduction signals (Barbosa *et al.*, 2021; Shoaib *et al.*, 2023). The fusion of nanomaterial (NMs) science and flexible electronics has led to the creation of wearable biophysical nanotechnology biosensors, capable of monitoring human activities, body movements, and electrophysiological signals like EEG and ECGs (Naresh & Lee, 2021). Wearable biosensors have the potential to revolutionize personalized healthcare and telemedicine. Chemical sensing, flexible materials, and scalable manufacturing processes have enabled wearables to monitor critical physiological indications such as temperature, vitals, bodily movements, and molecular biomarkers (Song *et al.*, 2021). Advancements in wireless communication and networking technology have enabled creative healthcare service designs. Wearable body area networks may send data using various wireless technologies. Wearable sensor nodes are placed throughout a wearable body area network to detect physiological signals. This comprehensive review will give updated information related to nanotechnology-enabled smart biosensors for monitoring and maintaining balanced health. Starting with a brief discussion of types of sensors such as chemical and biological sensors followed by their application in monitoring and detection of various aspects of health including the working mechanisms of various sensors. The next section covers the application of nanotechnology and NMs in the fabrication of smart biosensors. In this section, we have included nanorods, NPs, quantum dots, and nano-wired biosensors. Followed by safety requirements of chemical, biological, and wearable biosensors and lastly the current challenges and prospects of these biosensors.

2. CHEMICAL AND BIOLOGICAL SENSORS

Chemical and biological sensors are technologies based on microelectromechanical systems, designed as an alternative to expensive, complex analytical devices used for healthcare applications (Yang & Gao, 2019). Integration of these sensors in healthcare systems is considered an important benchmark of the healthcare sector and medical monitoring to enhance the quality of life. In the last five decades, use of the devices that detect analytes using optical, electrochemical, and piezoelectric transducers has progressed significantly (Tu *et al.*, 2020). These sensors consist of a recognition element coupled with a transduction element i.e., the chemical information in the receptor part is converted into a form of energy that is measured with the transducer. For example, concentration, pH, and sweat of the compound. The transducer translates the information into an analytical signal (Coyle *et al.*, 2014). Different analytes such as heavy metals along with spiropyran, oxazine, spirooxazine, and chromenes were identified for light-controlled receptors (Kumar *et al.*, 2019). The applications of photochromic sensors in the areas of specific recognition and multi-analyte discrimination, based on their isomerization to light, as well as pH, temperature, and solvent, were reported by Meng Qin for photothermic sensors (Qin *et al.*, 2015). In one review reported by Pedro Molina and coauthors, the advancements in highly selective anion receptors are explored, emphasizing the use of diverse noncovalent interactions such as halogen-bonding and anion-π interactions. It highlights the benefits of incorporating multiple binding sites for enhanced strength, selectivity, and interaction geometry in these receptors (Molina *et al.*, 2017). Photochromic molecules with positively charged spiro carbon are frequently used to detect toxic and biologically significant anions due to their ability to alter optical properties upon anion binding. These molecules can be easily modified to create anion coordination sites, enabling effective monitoring of anionic pollutants (Kumar & Kumar, 2023). In another study, a merocyanine salt form of a substituted spiropyran

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was developed for anion detection by Kumar and coworkers, utilizing HSO4-induced aggregation and light-responsive switching between the open merocyanine and closed spiropyran forms. This process led to the reversible release of hydrogen sulfate ions, with dynamic light-controlled aggregation monitored via DLS and TEM. The study demonstrates the first highly selective, reversible, and nanomolar-level response to HSO_4^- in water (Kumar & Kumar, 2023). A benzothiazolinic spiropyran was synthesized and characterized, showing that its colored merocyanine form forms H-aggregates in the presence of formic acid. This color change enabled the development of a smartphone-assisted sensing process with nanomolar sensitivity to formic acid (Kumar *et al.*, 2021).

Chemical sensors

Chemical sensors are vital tools for identifying and measuring certain chemicals or chemical compounds in a variety of settings, from the industrial to the biological. They are essential for keeping an eye on food safety, facilitating environmental assessments, detecting illnesses, and monitoring air quality (Arakawa *et al.*, 2022). Advances in electronics, materials science, and nanotechnology have propelled the growth of chemical sensors, resulting in increasingly sensitive, selective, and portable devices. Chemical sensors function primarily based on chemical recognition, which is the process by which a particular interaction between an analyte (the target mol-ecule) and a sensing element results in a signal that can be measured (Kim *et al.*, 2023). Changes in electrical conductivity, optical characteristics, mass, or electrochemical potential are only a few of the mechanisms that may be involved in this interaction. Chemical sensors comprise a broad spectrum of technologies that are necessary for material detection and quantification in a variety of applications. Electrochemical sensors are perfect for portable devices like glucose monitors because they can quickly and economically detect biomolecules, ions, and gases by measuring electrical changes at electrode surfaces (Yoon *et al.*, 2020). Optical sensors are essential for real-time monitoring of biological samples because they provide highly sensitive and non-invasive detection through the use of changes in light absorption, fluorescence, or refractive index. In environmental monitoring and medical diagnostics, piezoelectric sensors accurately measure analyte concentrations by converting chemical interactions into mechanical stress changes on a crystal surface. Gas sensors are essential for industrial safety and environmental assessment because they measure changes in electrical conductivity on semiconductor surfaces to detect gases like carbon dioxide and volatile organic compounds (Yaqoob & Younis, 2021). Colorimetric and Fluorescence-Based Detection of Mercuric Ion Using a Benzothiazolinic Spiropyran was carried out by Kumar and coworkers (Kumar *et al.*, 2019).

Different biosensors have been described as timesaving and end-user analytical techniques for the de-tection of numerous analytes such as clinical, food and environmental analytes within the past 60 years. Professor Leland C. Clark used glucose oxidase trapped in a dialysis membrane over a Clark-type oxygen electrode to publish the first example of an enzyme electrochemical biosensor (1962). Additionally, Guilbault and Montalvo described using urease in conjunction with glass electrodes to quantify urea concentration by potentiometry. Apart from these initial instances, DNA, enzymes, and antibodies have been paired with electrochemical transducers as components of biochemical recognition. These days, they make up the biggest group of biosensors used in en-vironmental, therapeutic, and food-sensing applications (Bollella & Katz, 2020).

Biological sensors

By incorporating nanotechnology, biological sensors are revolutionizing the detection and analysis of biological analytes, offering unprecedented sensitivity and specificity. The performance of these sensors is enhanced by leveraging nanoscale materials and techniques, allowing them to be used in various fields such as medical diag-nostics, environmental monitoring, and biotechnology (Lu *et al.*, 2023; Mohankumar *et al.*, 2021). The principle relies on the utilization of bioreceptors and a transducer to identify specific analytes and convert them into signals that can be measured. Enzymes, antibodies, nucleic acids (DNA/RNA), cells, or biomimetic materials can serve as bioreceptors, interacting specifically with target molecules. When the bioreceptor attaches to the analyte, it initiates a signal transduction process that generates an output, like electrical, optical, or mechanical signals. These signals are then measured and examined to determine the concentration or existence of the analyte. There are several types of biological biosensors available and utilized according to use (Kim *et al.*, 2019). Enzymatic biosensors utilize enzymes as bioreceptors to catalyze reactions and detect specific analytes, benefiting from nanotechnology's integration with NPs or nanowires to enhance sensitivity and speed (Daurai *et al.*, 2023). For example, glucose biosensors employ glucose oxidase on NMs surfaces, with NPs amplifying signals for rapid glucose detection in clinical settings (Cash & Clark, 2010). Immunological biosensors leverage antibodies or antigens immobilized on nanostructured surfaces to increase binding capacity and sensitivity, crucial for medical diagnostics, environmental monitoring, and food safety (Valenzuela-Amaro *et al.*, 2023). DNA biosensors, employing DNA strands functionalized onto NMs like graphene or carbon nanotubes, achieve high specificity in detecting genetic sequences or pathogens, supporting applications in genetic analysis and environmental moni-toring (Abu-Salah *et al.*, 2015). Whole-cell biosensors utilize NMs-enhanced cells to detect pollutants or toxins in real-time, essential for monitoring water quality and industrial processes. In medical diagnostics, environmental monitoring, and food safety, nanotechnology-enabled biological sensors play pivotal roles in advancing precision medicine, sustainable resource management, and public health protection.

3. DESIGN AND PRINCIPLE OF WORKING OF BIOSENSORS

The design and principle of biosensors typically involve several key components the summarized information on design and principles is as follows (Naresh & Lee, 2021) (Fig. 1).

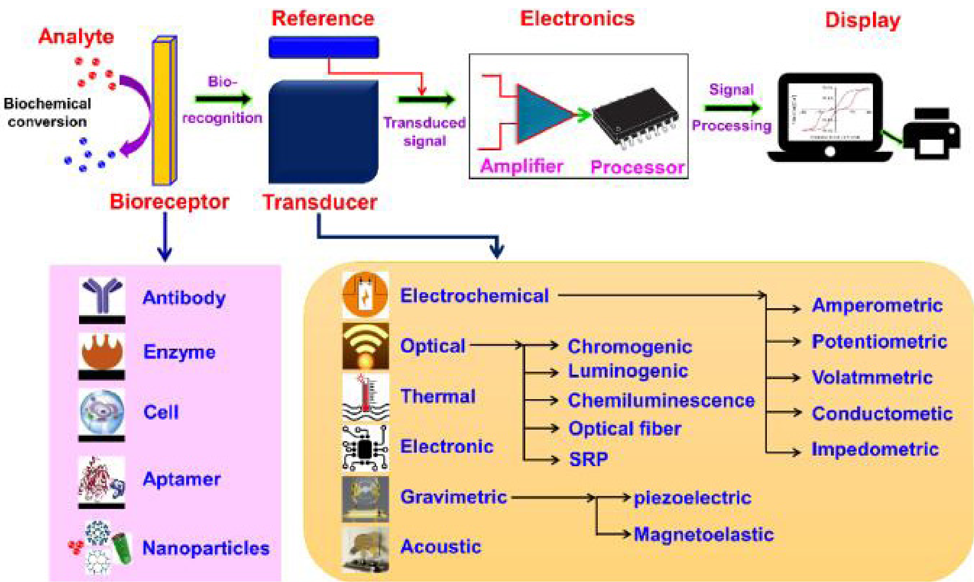

Figure 1. Illustration of design, principle, and type of detection method employed for biosensors. Adapted from (Naresh & Lee, 2021) under Creative Commons Attribution (CC BY) license).

The biological recognition element: It is in charge of interacting with the target analyte in a certain way. The type of analyte being detected can involve an enzyme, antibody, nucleic acid, cell receptor, or entire cell. The biosensor gains specificity from the bio-recognition element, which exclusively binds to the intended analyte which produces a detectable signal.

Transducer: The transducer creates a quantifiable signal from the biological reaction brought about by the contact of the analyte and the recognition element. Thermal, optical, electrochemical, and piezoelectric transducers are examples of common transducer types. The selection of a transducer is contingent upon various aspects, including the biosensor's intended use, sensitivity specifications, and detection methodology.

Signal processing system: Biosensors often incorporate a signal processing system to amplify, process, and analyze the signal generated by the transducer. Signal processing may involve amplification techniques, signal filtering, digitization, and data analysis algorithms to enhance the accuracy and reliability of the biosensor's output.

Interface: The interface facilitates communication between the biological recognition element, transducer, and signal processing system. It ensures the efficient transfer of the biological response into a measurable signal and may include immobilization techniques to securely attach the biological recognition element to the transducer surface.

The operation of a biosensor follows a general principle, which involves the following steps:

Recognition: The biological recognition element that is immobilized on the sensor surface interacts selectively with the target analyte present in the sample. A binding event or biochemical reaction unique to the target analyte is produced as a result of this contact.
Transduction: The transducer converts the biological reaction which is the product of contact between the recognition element and an analyte into a signal that can be measured. Depending on the kind of transducer being utilized, the signal may be optical, electrochemical, acoustic, or thermal.
Signal processing: To obtain pertinent data regarding the concentration or existence of the target analyte, the signal processing system amplifies, processes, and analyses the transduced signal. For signal processing algorithms to increase the precision and dependability of the biosensor's output, calibration processes, background removal, and noise reduction strategies may be used.
Output: The final output of the biosensor is typically a quantitative measurement of the target analyte concentration or a qualitative indication of its presence. This output can be displayed directly on the biosensor device or transmitted to external data acquisition systems for further analysis and interpretation.

4. NON-INTERVENTION CHEMICAL SENSORS AND BIOSENSORS

Non-interventional chemical sensors are designed to detect and analyze specific chemical compounds or elements in a sample without altering its composition. They play a crucial role in various fields such as environmental monitoring, industrial process control, and medical diagnostics.

4.1. Non-interventional chemical sensors

These sensors detect and quantify chemical compounds or biomarkers in bodily fluids or excretions without requiring direct contact with the body. They often provide real-time monitoring capabilities and are useful for tracking changes in health status over time.

Example: wearable sweat sensors

Wearable sweat sensors are emerging as powerful tools for non-invasive health monitoring. These sensors collect sweat from the skin and analyze its composition to provide insights into an individual's hydration status, elec-trolyte balance, and overall health. One notable example is the Gatorade Gx Sweat Patch, developed by Gatorade in collaboration with scientists and engineers. The Gx Sweat Patch is a disposable, single-use patch worn on the skin during physical activity. It contains microfluidic channels and sensors that capture sweat and measure key electrolytes, including sodium, chloride, and potassium, as well as sweat rate (Kaya *et al.*, 2019).

For example, consider a non-interventional chemical sensor used for detecting airborne pollutants. Such a sensor, integrated into a smart air quality monitoring system, employs optical or electrochemical techniques to measure levels of harmful gases like nitrogen dioxide or volatile organic compounds. By placing these sensors in urban areas or industrial sites, they continuously collect data on air quality without requiring manual sampling or direct contact with the pollutants. This real-time data helps in assessing pollution levels and implementing timely interventions to protect public health and improve environmental quality (Yaroshenko *et al.*, 2020).

4.2. Non-interventional biosensors

Biosensors incorporate biological components such as enzymes, antibodies, or cells to detect specific biomolecules or analytes in biological samples. These sensors offer high sensitivity and specificity and are widely used in healthcare for diagnostic purposes and monitoring of disease progression.

Non-interventional biosensors offer a groundbreaking approach to health monitoring by providing real-time, passive detection of physiological parameters without the need for invasive procedures.

These devices use ad-vanced materials and technologies to measure biomarkers such as glucose, lactate, or dehydration levels from body fluids or environmental conditions, making them ideal for continuous health tracking.

A notable case study involves the development of a non-interventional glucose biosensor designed for diabetics. This biosensor, integrated into a wearable patch, utilizes electrochemical sensors to monitor glucose levels through interstitial fluid. It continuously transmits data to a smartphone application, allowing users to manage their glucose levels effectively without frequent finger-pricking. This technology not only enhances patient comfort but also improves disease management by providing real-time feedback and facilitating better glycemic control, thereby demonstrating the significant potential of non-interventional biosensors in personal health care (Johnston *et al.*, 2021).

Continuous glucose monitoring systems continuously monitor the increase or decrease in glucose level of an individual with diabetes by measuring the glucose concentrations in interstitial fluid. The sensor, typically inserted subcutaneously, detects glucose levels and transmits data wirelessly to a receiver or smartphone. This allows patients to track their glucose levels in real-time and adjust insulin dosages accordingly. Examples include the Dexcom G6 and Abbott's Freestyle Libre, which provide non-interventional glucose monitoring, reducing the need for frequent fingerstick tests and enhancing patient comfort and convenience (Freckmann, 2020).

5. UTILIZATION OF CHEMICAL AND BIOLOGICAL SENSORS IN MONITORING VARIOUS ASPECTS OF HEALTH

Biosensor applications in the field of medical science are expanding quickly. In clinical settings, glucose biosensors are frequently employed to diagnose diabetes mellitus, a condition that necessitates exact control over blood glucose levels. 85% of the enormous global market is accounted for by home use of blood-glucose biosensors. In the medical field, biosensors are widely employed for the diagnosis of infectious diseases. Research is being done on a potential biosensor technology that can diagnose urinary tract infections (UTIs) and identify pathogens and antimicrobial susceptibilities. It is crucial to identify individuals with end-stage heart failure who are at risk of negative outcomes during the initial stages of left ventricular aided device placement. Hafnium oxide-based new biosensor has been applied to the early recognition of the human interleukin (IL)-10. The study examines the relationship between recombinant human IL-10 and a monoclonal antibody to detect cytokines early following device placement. The interaction between the antibody and the antigen is characterized by fluorescence patterns as well as electromechanical impedance spectroscopy, with fluorescence patterns facilitating protein bio-recognition. HfO_2 is a bio-field-effect transistor with extreme sensitivity. When a human antigen is detected using electrochemical impedance spectroscopy, the HfO_2 biosensor is ready for antibody deposition (Mehrotra, 2016).

5.1. Voltametric biosensors

Voltametric biosensors stand as a revolutionary advancement in healthcare, offering a trifecta of rapidity, sensitivity, and precision in detecting crucial biomolecules essential for diagnosing diseases, monitoring treatments, and managing patients' conditions. By amalgamating electrochemistry with biological recognition elements, these biosensors herald a new era of point-of-care testing across various medical domains. Their impact is most pronounced in the realm of glucose monitoring for diabetic individuals, where they furnish real-time measurements devoid of the discomfort associated with invasive blood sampling. However, their utility extends far beyond glucose detection. Voltametric biosensors excel in identifying disease biomarkers, spanning proteins, enzymes, and nucleic acids, thereby facilitating early diagnosis and prognosis of ailments like cancer, cardiovascular diseases, and infectious illnesses (Kimmel *et al.*, 2012). Their significance amplifies in settings with limited access to conventional laboratory facilities, as they offer portability, swiftness, and accuracy essential for decentralized healthcare delivery. Furthermore, ongoing advancements in nanotechnology and miniaturization are propelling voltammetric biosensors to newer heights, promising broader applications in personalized medicine, drug development, and telemedicine (Liu *et al.*, 2022). In essence, voltammetric biosensors are poised to perpetuate their transformative impact on healthcare, empowering both clinicians and patients with actionable diagnostic insights for optimized health outcomes.

5.2. Potentiometric biosensors

Potentiometric biosensors have emerged as indispensable assets in modern healthcare, offering swift, sensitive, and precise detection of vital biomolecules essential for diagnosing diseases, monitoring treatments, and man-aging patient conditions. Leveraging the principles of potentiometry, these biosensors gauge changes in electrical potential resulting from biochemical interlinks of the target analyte and the recognition element affixed to the electrode surface. In the realm of medical diagnostics, potentiometric biosensors play a pivotal role in accurately quantifying biomarkers linked to a spectrum of diseases, encompassing diabetes, cardiovascular disorders, infectious diseases, and cancer (Bratov *et al.*, 2010). Their capability enables early disease detection and facilitates the design of tailored treatment regimens, ultimately enhancing patient outcomes. The portability, user-friendliness, and rapid response time of potentiometric biosensors renders them ideally suited for point-of-care testing, bringing diagnostic capabilities directly to the patient and streamlining turnaround times for critical decisions. This accessibility is particularly beneficial in remote or resource-limited settings, where immediate diagnosis and intervention are paramount. Continual advancements in nanotechnology, materials science, and bioengineering hold the promise of expanding the horizons of potentiometric biosensors (Sadak, 2023).

5.3. Enzymatic sensors

Enzymatic biosensors utilize biological materials, typically enzymes, to detect specific substances through en-zymatic reactions. These sensors undergo reversible reduction or oxidation on the electrode when an electro-chemically active potential is applied. They are categorized into inhibitor sensors, which assess enzyme activity inhibition, and substrate sensors, which detect specific substrates and monitor their enzymatic conversion. En-zymatic biosensors offer rapid, sensitive, and selective detection, which make it the precious tools in various fields, including healthcare, environmental monitoring, and industrial processes. Inhibitor and substrate sensors are two more subcategories of enzyme sensors. Substrate biosensors typically identify specific substrates and their enzymatic processes, whereas inhibitor sensors frequently measure the reducing activity of the enzyme or com-pounds (Singh *et al.*, 2020).

6. NANOTECHNOLOGY IN THE FABRICATION OF SMART BIOSENSORS

Nanotechnology has been considered an emerging field in developing the devices at nano level employing various NMs that are integrated with the biomolecules or analytes for which biosensors are intended to be used (Mao *et al.*, 2018). As these BSs have stand-alone properties such as magnetic, electrical, and optical properties so, these can be used for different bioengineering applications and drug delivery systems (Mao *et al.*, 2018). The application of nanotechnology with biosensing devices can offer various advantages including surface-to-volume ratio alternation of biological transduction and signaling mechanism with significant electrochemical properties (Rizwan *et al.*, 2022). The advances in nanotechnology allow to building of structures in nano-regime, such as NPs, nanowires, and nanotubes which directly probe and interact with various biomolecules, which can detect and interact with respective biomolecule that intend to detect using biosensors. The nano biosensors can assess the specific analytes and get detailed information regarding the various diseases. The accurate sensing enables the sensing of various fluctuations providing disease indication, its progression, and therapeutic assessment (Purohit *et al.*, 2020). Numerous reviews are reported on an understanding of specific nanostructures used for biosensors. Cho *et al.* summarized the various categories of NMs such as metallic, carbon nanotubes, silica, organic polymers carbon allotropes, and non-carbon NMs as an alternative component of the electrode and enhanced electrochemical properties of biosensors (Cho *et al.*, 2020). Various methodologies adopted for the development of nanotechnology-assisted biosensors are discussed as follows:

6.1. Lithographic techniques

Lithographic techniques are used to create the biosensors as they can produce the micro or nano complex using higher resolution topography with localized deposition of molecules for preserving bioactivity. Lithographic techniques are further categorized as photolithography and electron beam lithography. In photolithography, microfluidic with a droplet generator and pico-injector is developed with a microfluidic chip that targets the DNA that underwent amplification and exhibits the fluorescence signal (Fruncillo *et al.*, 2021). In electron beam lithography, the nanosized biosensors were fabricated on a flat surface covered with electron beam-sensitive material by focusing an electron beam to generate the customized nanopatterns (Kurt *et al.,* 2021). The litho-graphic techniques yield ultra-sized nanopattern ranges these techniques are widely applied in the healthcare domain for the diagnosis of diseases. The growing demand and overcoming the limitations of lithography such as high energy consumption, and complexity raised the need to develop an alternative technique that is flexible and cost worthy. Table 1 gives a summary of the advantages and limitations of conventional and advanced litho-graphic techniques (Stokes *et al.,* 2023).

6.2. Electroplating technique

Electroplating is the process of depositing metal ions, propelled by an electric current, onto a conductive surface from an electrolyte solution. This process's capacity to precisely alter surface characteristics makes it very bene-ficial for the creation of biosensors (Stine, 2019) . Electroplating is a regularly used technique in biosensors to provide uniform and smooth metal coatings on electrodes, improving their conductivity and offering a strong foundation for further functionalization stages. For example, electrodes composed of noble metals, such as platinum or gold, can be electroplated to increase their surface area, which can boost the effectiveness of biomolecule immobilization and improve sensitivity to analytes (Zhu *et al.,* 2015). Additionally, electroplating makes it possible to deposit particular metals or alloys onto sensor surfaces, which makes it easier for biomolecules like enzymes or antibodies to adhere to the surface (Pandit *et al.,* 2023). Gives biosensors selectivity, enabling them to identify and attach to target analytes with specificity. This improves detection accuracy in a variety of applications, including environmental monitoring and medical diagnostics.

6.3. Surface treatment by plasma

Exposure of material surfaces to a low-temperature plasma discharge is a versatile approach known as surface treatment by plasma. Ionized gases, or plasma, interact with molecules on the surface to modify their shape and chemistry without appreciably changing the bulk properties (Dowling *et al.,* 2011; Hirohata & Takanashi, 2014). Plasma treatment has several uses in the context of biosensors. First, it cleans surfaces by eliminating organic residues and impurities, leaving them immaculate for further processing stages (Salmani Rezaie *et al.*, 2016). Additionally, plasma stimulates surfaces by adding reactive functional groups like amino or hydroxyl groups, which increase the surface's affinity for attaching biomolecules. The stability and effectiveness of the biomolecular layers in biosensors are improved by this activation procedure, which boosts sensor performance (Naresh & Lee, 2021). Furthermore, surfaces can be roughened or selectively etched by plasma treatment, which is advantageous for improving surface topography and the adherence of thin films or functional coatings. All things considered, plasma surface treatment is a versatile and eco-friendly method of surface modification that can be used on a variety of materials, such as metals, polymers, and ceramics (Banerjee *et al.,* 2021). It is also crucial for improving the sensitivity, selectivity, and dependability of biosensors in a wide range of applications.

6.4. Chemical vapour deposition

Thin film materials are deposited onto surfaces using the chemical vapor deposition (CVD) process, which in-volves gaseous phase chemical reactions. It is possible to precisely regulate the thickness, homogeneity, and composition of films using CVD techniques, which makes them perfect for creating functional coatings and incorporating NMs onto biosensor platforms (Dede & Altay, 2018). CVD is used in biosensor applications to create thin films on sensor surfaces that function as barrier coatings, protective layers, or active components. By altering surface characteristics like hydrophobicity, biocompatibility, or chemical reactivity, these thin coatings can improve the stability and selectivity of sensors. Moreover, CVD permits direct growth of nanoscale objects on sensor surfaces, such as carbon nanotubes, graphene, or nanowires (Rajesh *et al.*, 2021). These nanostructures are ideal for improving sensor sensitivity and enabling innovative sensing processes because of their distinctive qualities, which include high surface area, superior electrical conductivity, and certain chemical capabilities. The capabilities of CVD are further expanded by variations like atomic layer deposition and plasma-enhanced CVD (PECVD), which provide fine control over deposition rates and film properties —a necessary component for incorporating cutting-edge materials into biosensor designs.

All things considered, CVD methods are essential to the advancement of biosensor technology since they allow sensors with improved performance characteristics to be developed for use in environmental monitoring, medical diagnostics, and other fields (Oke & Jen, 2022).

Technique	Principal	Resolution	Advantages	Limitations
Conventional techniques				
Electron beam lithography	Electron pattern resist	>10 nm	Precise control, Pattern complex geometric	Possible damage to the sample, complex and costly procedure
UV lithography	UV light masks the pattern with a photo-resistant	100 nm to 1000 nm	Simple, efficient, mass produc-tion	Clean room requi-red, interfer-ence effects, the subs-trate must be flat
Soft lithography	Elastomeric mold to fa-bricate and replicate the structure	35 nm	Substrate flatness is not critical	Clean room required, costly, removing the stamp from mold may create damage
Scanning probe lithography	The sharp tip changes the structural or che-mical proper-ties of the surface	4-10 nm	Cost efficient, Substrate need not require fur-ther development	Low throughput
Advanced techniques				
Immersion lithography	The use of UV light masks the pattern to photoresist, and trans-parent liquid is placed between the apparatus photoresist	38 nm	Improved resolution	Fluid concentration, contain-ment-free fluid required
Nanosphere lithography	The patterning is done with a colloidal crystal mask, gener-ated from nanospheres.	1-10nm	Low-cost, ver-satile, contro-lled structures formed	Difficult to con-trol the crystal morphologies
Nanoimprint lithography	Polymer is spin-coated onto a substrate and a stamp is pushed down onto it	< 3nm	Precise, high throughput, cost worthy	Pattern replication defects may occur

Table 1. Summary of the advantages and limitations of conventional and advanced lithographic techniques

6.5. DNA/RNA structure-based fabrication

In this nanotechnology-based technique, the base pairing language is used to generate the nanostructure and further manipulated at the nanoscale. The technique extensively applies to the nanomachines for gene editing, molecular computing, and biosensing (Xiao *et al.*, 2019). The technique enables the construction of DNA nanostructure devices that sense the singles and imagine the molecules. The binding of nucleic acid structure to analytes induces structural modifications, which ultimately shows the signal readouts via the hybridization of nucleic acids. As the use of DNA-based techniques is considered an emerging technique, various reviews are published that give summarized information and their applications for the detection of viral diseases (Chandrasekaran, 2017; J.-e. Kim *et al.*, 2023; Ma *et al.*, 2021; Yuwen *et al.*, 2023).

7. NANOMATERIAL ADDED INTELLIGENT BIOSENSOR

NMs-enhanced intelligent biosensors represent a breakthrough technology at the intersection of nanotechnology and biosensing, offering unparalleled capabilities in detecting target analytes with high sensitivity, selectivity, and speed. By incorporating NMs such as NPs, nanowires, or nanotubes into biosensor designs, these innovative platforms harness the unique properties of nanoscale materials to enhance signal transduction mechanisms, increase surface area for biomolecular interactions, and enable rapid electron transfer processes (Fig. 2). This results in biosensors with exceptional performance characteristics, including the ability to detect analytes at ultralow concentrations, discriminate against interfering substances, and provide real-time or near-real-time measurement capabilities (Holzinger *et al.*, 2014). Moreover, the versatility of NMs allows for the customization of biosensors tailored to specific applications, ranging from medical diagnostics and environmental monitoring to food safety and homeland security. With their miniaturization potential and compatibility with portable and integrated devices, NMs-enhanced intelligent biosensors hold promise for transforming various fields by enabling on-demand, point-of-care testing, and decentralized analytical capabilities (Pirzada & Altintas, 2019).

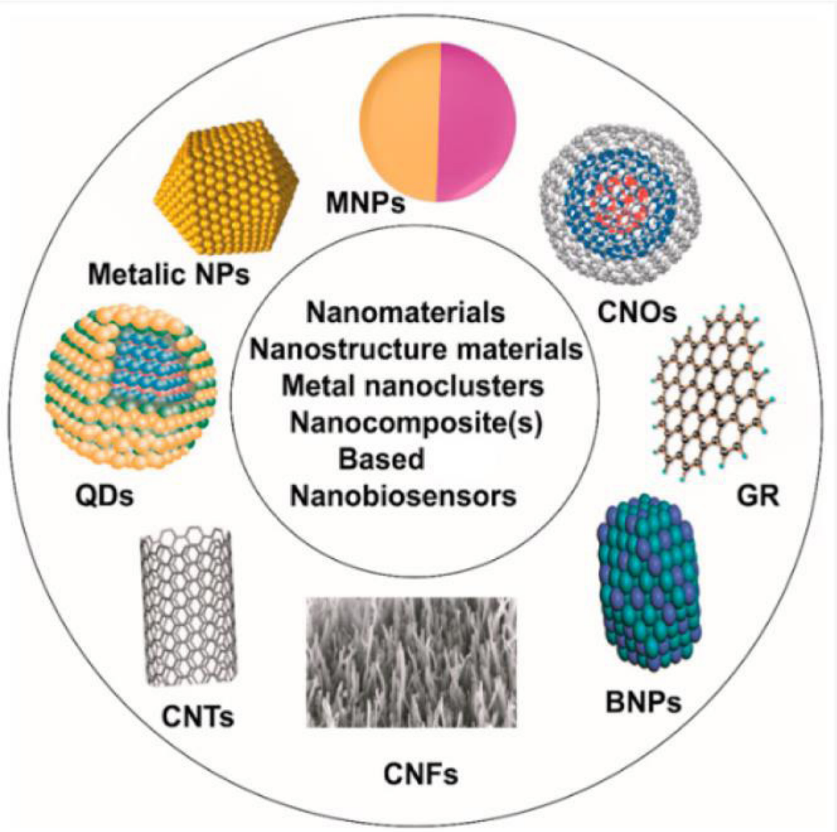

Figure 2. Illustration for Nanomaterial added intelligent biosensor. Adapted from (Hassan, 2022) under CCBY-4.0.

7.1. Metal oxide enabled biosensor

Metal oxide-enabled biosensors represent a cutting-edge class of sensing devices that utilize metal oxide materials, such as zinc oxide (ZnO), titanium dioxide (TiO_2), and tin oxide (SnO_2), as the sensing elements. These biosensors exploit the unique electrical, optical, and surface properties of metal oxides to detect and quantify target analytes with high sensitivity and selectivity. Metal oxide nanostructures provide large surface areas and abundant active sites for biomolecular recognition, facilitating enhanced interactions with target molecules and promoting efficient signal transduction mechanisms (Liu & Liu, 2019). Furthermore, the tunable properties of metal oxides, such as bandgap engineering and surface functionalization, enable the customization of biosensors for specific applications, including medical diagnostics, environmental monitoring, food safety, and homeland security (Kishore Kumar *et al.*, 2020).

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7.2. Nanowire-based biosensors

Nanowire-based biosensors utilize semiconductor nanowires as the sensing element for ultrasensitive detection and analysis of biomolecules. These nanoscale devices operate on principles such as electrical, optical, or me-chanical transduction, where biomolecular interactions on the nanowire surface induce measurable changes in electrical conductance, optical properties, or mechanical resonance (Ambhorkar *et al.*, 2018). Surface func-tionalization of nanowires with biorecognition molecules enables selective binding to target analytes, facilitating specific detection. Nanowire biosensors offer advantages including high sensitivity, real-time detection, multi-plexing capability, and potential integration into miniaturized, portable devices, making them promising tools for applications in medical diagnostics, environmental monitoring, and drug discovery (Wanekaya *et al.*, 2006).

7.3. Nanorods-based biosensors

NRs are rods having dimensions ranging from 1 to 100 nm and are synthesized chemically from different mate-rials such as graphene, graphene oxide, oxides of various metals, and other semiconducting materials. These NRs have shown excellent potential in the field of biosensing for the detection of nucleic acids, different carbohydrates, metal ions, etc. Nanorod-based biosensors leverage the unique properties of semiconductor nanorods as the sensing platform for highly sensitive and specific detection of biomolecules. These nanoscale devices employ diverse detection mechanisms, including electrical, optical, and mechanical transduction, wherein biomolecular interactions on the nanorod surface induce measurable changes in conductance, optical properties, or mechanical resonance. Surface functionalization of nanorods with biorecognition molecules enables selective binding to target analytes, facilitating precise detection. Nanorod BSs provide notable benefits such as enhanced sensitivity, rapid response times, and compatibility with miniaturized, portable devices, making them promising tools for applications spanning medical diagnostics, environmental monitoring, and biodefense (Naresh & Lee, 2021).

7.4. Dendrimer-based biosensors

Dendrimers have attracted a lot of interest lately as adaptable nanoscale structures with potential uses in the biosensor industry. Three-dimensional hyperbranched macromolecules known as dendrimers provide a special set of characteristics, such as high branching densities, variable surface functions, and well-defined topologies. They are hence ideal for developing biosensing platforms with improved stability, selectivity, and sensitivity. Den-drimers' multifunctionality is leveraged in biosensor design through their inclusion (Satija *et al.*, 2011). Bio-molecules including nucleic acids, enzymes, and antibodies can be immobilized using dendrimers as molecular scaffolding. Target analytes interact with these recognition components more effectively because of the regulated immobilization that preserves their bioactivity and makes it easier for them to be precisely arranged. Applications for dendrimer-based biosensors can be found in many different fields, such as food safety, environmental monitoring, and medical diagnostics (Modi *et al.*, 2023).

7.5. Quantum Dots

Semiconductor NPs that offer bright fluorescence and size-tunable emission properties, enhancing detection sensitivity and multiplexing capabilities. Quantum dots (QDs) are widely used in biosensors due to their excep-tional quantum yield and photoluminescence. Carbon quantum dots offer additional benefits such as enhanced solubility, reduced toxicity, and simpler synthesis compared to traditional QDs, making them ideal for biomedical uses (Malhan *et al.*, 2024). With their zero-dimensional structure under 10 nm, carbon quantum dots exhibit excellent biocompatibility and unique optical properties, including high photoluminescence and quantum yield, positioning them as promising candidates for advanced biosensing and bioimaging applications (Pourmadadi *et al.*, 2023).

7.6 Carbon nanotubes

Cylindrical nanostructures with excellent electrical conductivity and large surface areas are useful for electro-chemical biosensors and facilitating rapid electron transfer. Carbon nanotube-based sensors are versatile, and used in electrochemical, optical, and field-effect applications for detecting food safety, heavy metals, and viruses. Despite their potential, few have reached the market due to challenges in integrating nanotube sensing elements into devices and scaling up fabrication for industrial use (Kumar & Kumar, 2023).

8. USAGE OF DIFFERENT NANOMATERIALS IN THE FABRICATION OF BIOSENSORS

NMs have recently received a lot of attention due to the necessity to manage the amount of chemicals in the human body and environment. Typically, NMs encompass at least 100 nm in size (Pawar *et al.*, 2024; Rajput *et al.*, 2024). NMs are now making tremendous development due to their vast potential uses in catalytic processes, technology, material science, structural elements, and biosensors. Advancements in NMs properties within nanoscale environments have led to the emergence of innovative devices, such as smart biosensors, capable of rapidly detecting the minute concentrations of the target bio-samples for real-time monitoring (Kulkarni *et al.*, 2022a). NMs are commonly employed as transducer material, which constitutes a key component in biosensor development. A biosensor is made up of four parts: a bioreceptor, a transducer, a signal processor that converts electronic signals to desired signals, and an interface for display. Biosensors may be used to analyze many substances, including bodily fluids, food, and cell culture (Malhotra & Ali, 2018). NMs, like NPs, nanorods, nanowires, carbon nanotubes, quantum dots, and dendrimers provide the option of boosting biosensor functionality and increasing detection power by controlling size and shape (Abdel-Karim *et al.*, 2020). Fig. 3.

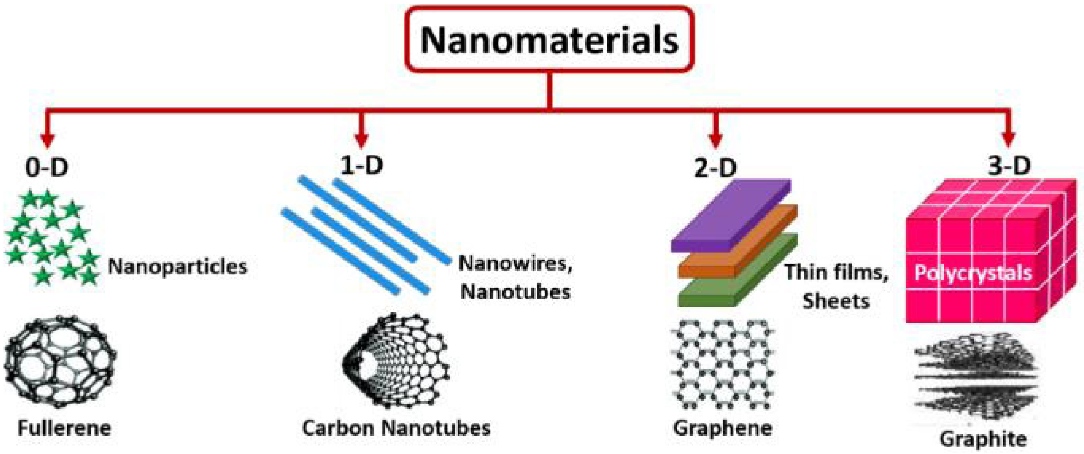

Figure 3. Different nanomaterials used in the fabrication of biosensors. Adapted from (Kulkarni *et al.*, 2022b) under CCBY 4.0

8.1. Nanoparticle-based biosensors

Due to their unique properties, NPs have found extensive use across diverse biomedical applications, including the development of biosensors for drug delivery, therapy, imaging, and medical diagnostics. The binding of target biomolecules profoundly influences their physical and chemical attributes, due to their minute size and shape. Excellent optical, electrical, magnetic, chemical, mechanical, and catalytic capabilities are exhibited by metal and noble metal NPs, such as gold (Au), silver (Ag), platinum (Pt), palladium (Pd), cobalt (Co), iron (Fe), and copper (Cu), as well as metal oxide NPs (ZnO, TiO_2, SnO_2, and MnO_2). Coating with different matrices, such as metal oxides, silica networks, polymers, graphene, fibers, and dendrimers, can customize the performance of NP bio-sensing (Maduraiveeran *et al.*, 2018). Noble metal NPs, with their remarkable size and shape-dependent chemical, physical and electrochemical properties play a key role in the progress of electrochemical sensor and biosensor platforms for *in vivo* and *in vitro* biomedical analyses. Metal oxide NPs are widely used in many different do-mains, including catalysis, soft magnetism, electrochemistry, sensors, and more (Nagime *et al.*, 2023; Nwabor *et al.*, 2020; Nwabor *et al.*, 2021; Ontong *et al.*, 2020; Puri *et al.*, 2023; Singh, Chunglok, *et al.*, 2022; Singh, Nwabor, *et al.*, 2022; Syukri *et al.*, 2020; Syukri *et al.*, 2021; Syukri *et al.*, 2024). Metal oxide NMs have the potential to greatly increase sensitivity and/or selectivity because of their massively decreased dimensions, large surface to volume ratio, and specific facet exposure. Because of their exceptional surface-to-volume ratio, chemical dura-bility, biocompatibility, excellent electrical conductivity and strong mechanical strength, carbon-based NMs

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such as graphene, bucky paper, single-walled carbon nano-horns, multi-walled carbon nanotubes, and fullerenes, etc., offer many important benefits. Gold NPs electrochemical sensors for sensitive uranyl detection in natural water were shown by Wu *et al.* designed sensor detected uranyl in the range of 2.4 to 40 µg/L, and anodic stripping voltammetry gives the yield, the LOD, 0.3 µg/L (Shi *et al.*, 2021). A graphitic carbon nitride modified with Pt and zinc oxide NPs was produced by Dharuman *et al.* for nonenzymatic glucose sensing, offering a broad detection of 250 µM to 110 mM. In whole blood, it may be reused four times, and in blood serum, eight times (Imran *et al.*, 2021).

8.2. Graphene-based biosensors

Graphene, often known as "carbon-sheets," is a two-dimensional carbon structure with sp2 hybridization. These sheets can be rolled in to create nanotubes or stacked horizontally to create a three-dimensional graphite structure. Due to its higher surface-volume ratio, low charge carrier resistance, and excellent conductivity, graphene is a great option for a transducing material (Sengupta & Hussain, 2021). Graphene field-effect transistors stand out among other graphene-based biosensing systems because of their ultrasensitive and low-noise detection capabilities, which enable immediate readings even in the presence of minute quantities of analytes. Because graphene's vast surface area facilitates the presence of many imperfections that serve as electro-active sites for heterogeneous electron transport, graphene is commonly employed in electrochemical biosensors. A silver NPs-graphene-chitosan nanocomposite was employed by Huang *et al.* to detect the avian influenza virus, with a 1.6 pg/mL detection limit (Huang *et al.*, 2016). A graphene-polymer-based electrochemical biosensor was em-ployed by Navakul *et al.* to detect viruses as low as 0.12 PFU/mL (Navakul *et al.*, 2017). GFET-type biosensors will be the best feasible biosensing technique for graphene, as graphene is a wonder material that has demonstrated via several pieces of evidence that it will surpass all hurdles in the future.

8.3. Carbon nanotubes

Allotropic carbon, or carbon nanotubes (CNT), is distinguished by its superior mechanical, electrical, electro-catalytic, and thermal characteristics. It may alternatively be described as a rolled-up sheet of graphene, and the number of constructed walls determines its characteristics. In the realm of biosensors, the unique shape of CNT has drawn a lot of potential applications (Simon *et al.*, 2019). In the domain of biosensors, CNTs have been suggested as a sensing element to identify and track several ailments, including bacterial infections and diabetes. Punbusayakul *et. al.*, (2013) used CNTs for the detection oil salmonella via electrochemical monitoring of the immune complex, which showed reduced detection time and made sample preparation. In another research, it was found that faster electron transport and increased sensitivity for electrochemical detection are made possible by the presence of CNT at the electrode surface (Wayu *et al.*, 2019). The most popular type of biosensors is CNT-based electrochemical ones that employ glucose oxide to detect glucose. Chen *et al.* modified carbonized silk fabric with Pt microspheres to create a very flexible MWCNT biosensor for glucose detection. One benefit of this biosensor was its electrode flexibility, which made it easier to use in wearable electronics (Lee, 2023).

8.4. Quantum dots

Fluorescent semiconductor nanocrystals, commonly referred to as QDs, are NPs with diameters below 1 nm and have garnered significant interest in modern biosensing technologies. QDs have been shown to have a high surface-to-volume ratio and remarkable charge-carrying transport capabilities, which might help the performance of a biosensor (Wei *et al.*, 2021). Because of quantum mechanical processes, QDs have optical and electrical characteristics that differ dramatically from normal bulk materials. These characteristics make QDs intriguing candidates for biosensing. In addition to these properties, QDs also outperform typical fluorescent material in terms of brightness and bleaching resistance (Farzin & Abdoos, 2021). QDs can now be coated with inert or biocompatible materials to offer functional groups for bioreceptor immobilization as well as to anticipate any toxicity problems. As a result, nearly a biomolecule may be attached to these nanocrystals as long as the photo-physical recombination process remains unaffected (Holzinger *et al.*, 2014). Based on their sensing characteristics, QDs are classified as fluorescent, bioluminescent, chemiluminescent, and photo-chemical. Kamaci *et al.* Developed a zinc oxide based QD biosensor for the detection of cysteine. The ZnO QD-based fluorescent biosensor showed a robust fluorescence for cysteine detection, with a linear range of 0.1 to 600 µm and a LOD of 0.642 µm (Kamaci & Kamaci, 2021). Taranova *et. al.*, to identify many antibiotics, including CAP, STM, ofloxacin (OFL), and fluoroquinolone compounds, simultaneously in milk, developed an immunochromatographic technique that used multicolor QDs as the signal probe. The LOD values for the standard immunoenzymatically test were much higher than those of OFL, CAP, and STM, which were 0.3, 0.12, and 0.2 ng/mL, respectively (Taranova *et al.*, 2015). In addition, the examples outlined about the usage of QDs in bioanalysis indicate that combining various NMs and their characteristics is a potential approach for developing novel, highly effective transduction mechanisms for biosensors in the future. The various nanostructures used for biosensing, including their transduction process, are summarized in Table 2.

Nanomaterial	Mechanism	Analyte	References
NPs	Electrochemical	Glucose	(Andreescu & Luck, 2008)
NPs	Optical	DNA hybridization	(He *et al.*, 2000)
CNT	Electrochemical	Nitric oxide	(Zhang *et al.*, 2011)
Graphene	Electrochemical	Phenol	(Liu *et al.*, 2013)
Quantum dots	Fluorescent	Glycoproteins	(Sang & Wang, 2014)
Quantum dots	Photo-electrochemical	DNA	(Wang *et al.*, 2014)

Table 2. Different types of NMs as a biosensor and their mechanism of transduction.

9. NANOMATERIALS-ENABLED WEARABLE SENSORS

An increasing number of people have given their healthcare more importance as their standard of living has increased. As of right now, standard methods for personal healthcare mostly rely on ancient techniques, which sometimes include time-consuming and inconvenient steps and large or heavy equipment. Furthermore, the invasive methods used to collect the detection samples will cause the patients discomfort and agony. Wearable sensors are being extensively researched for their potential to check health parameters continually, promptly, and correctly to increase the effectiveness and comfort of personal health monitoring. These sensors are linked to the tissue area in a conformal manner to capture or sense the mechanical, electrical, thermal chemical alternations of objectives. So, these sensors are considered as state of art technologies in healthcare monitoring (Guk *et al.*, 2019). Many wearable sensors have been investigated as far as personal healthcare. Numerous research has examined the noninvasive methods of determining blood glucose concentration by measuring the amount of glucose in sweating, saliva, or tears. The state of our internal environment and its homeostasis can also be indicated by the pH and the concentration of various ions (K^+, Na^+, Cl^-, Cu^{2+}, Zn^{2+}, Pb^{2+}, etc.) in sweat or other bodily fluids. Furthermore, to achieve the simultaneous detection of numerous parameters and correct for the inaccurate results caused by temperature, wearable temperature sensors are typically constructed and coupled with other sensors (Majumder *et al.*, 2017). Wearable sensors are considered as key tool for the healthcare system but, they have high specificity, stability, and sensitivity requirements. Wearable sensors' sensing components should have outstanding conductivity to convert a variety of signals into electrical signals. All these features guarantee that the wearable sensors can identify small variations in an individual's movement or the molecules and ions in bodily fluids. Thus, the creation of wearable sensors has made use of functional materials. Because of their large aspect ratio, high conductivity, and quick electron transfer kinetics, NMs are a prevalent choice among all, which can significantly improve the functionality of wearable sensors (Peng *et al.*, 2020). NMs can be categorized into various classes, and based on their fabrication method these are synthesized with varying dimensions. 0D, 1D, and 2D for metallic carbon nanotubes, metallic nanowires, and graphene and transitional metals nanosheets, respectively. As per the percolation theory, nanowires, nanotubes, and nanofibers are considered effective in forming the conductive path compared to metallic NPs. NMs-enabled wearables are formed by depositing the NMs on the surface of a polymer matrix. As this is a complex process, the distribution of material fillers has an important role in maintaining the electrical and mechanical properties of sensors (Phan *et al.*, 2022). Regulated blood pressure (BP) and heart rate are considered vital signs in healthcare monitoring as the increase or decrease in the level of BP leads to abnormalities. The gold standard for continuous blood pressure monitoring is arterial catheterization, although it is intrusive and usually reserved for very sick patients. While sphygmomanometers are less intrusive, they have several drawbacks, including non-portability and inconsistent readings. In this sense, it is anticipated that wearable flexible sensors would open new avenues for telemedicine's future of remote health monitoring. Wang *et al.* (2018) describes a wearable sensor patch for checking the BP. The piezoelectric component and thin Si layers were used as sensing elements and elastomers. The use of this elastomer showed deeper penetration for BP detection additionally, the use of this type of sensor reveals the superior properties for long-term monitoring of BP with 60% stretchability, 23.6mW power consumption, and equal to 5Pa loading pressure skin layer. Furthermore, the wearables for electrophysiological sensors are related to bioelectric signals. The use of electrocardiogram (ECG) and electromyogram (EMG) gives information on muscle tissue, nerve tissue, and related activity which is used in the diagnosis of neuromuscular disorders. However, these devices utilize wet electrodes which are unstable for measurement leading to deteriorated signal quality and repeated application of gel needed. so, the development of gel-free wearables plays a vital role in diagnosis with significant improvement in detection. Yao *et al.* summarized the use of different NMs-based wearables that can show promising potential as they have a good electrical interface between the electrode and skin. The different type of NMs, their comparison, and other miscellaneous examples are described in the given review. Li *et al.* (2019) presented a novel integrated stretchable hybrid SEP with the electrode and liquid metal interconnect galinstan into the elastomer matrix for ECG heart monitoring. It reveals, with the CMOS fabrication method, low-power, and high-performance ECG chips show a signal output of 100 mV. Additionally, external environmental protection gives better results.

Metallic NMs (Au, Ag) are reported as emerging structures in the field of biosensing. Various investigations are reported on the use of Au/Ag-based biosensors in viral diseases as reliability and biocompatibility make them potential candidates for diagnosis. Aedes aegypti mosquitoes carry the dengue virus, an arthropod-borne virus disease that poses serious health hazards in tropical and subtropical regions of the world (Fritea *et al.*, 2021). The primary method of examining dengue virus is by clinical symptoms, which are then verified by laboratory tests such as reverse transcription polymerase chain reactions, enzyme-linked immunosorbent assays (Alzagameem *et al.*), point-of-care testing, immunoglobulin G, and immunoglobulin M (Peeling *et al.*, 2010). Nevertheless, the previously described methods are costly, time-consuming, and need a specialized individual. Conversely, the localized surface plasmon resonance sensor was investigated as an inexpensive, quick, and trustworthy instrument for label-free detection. Label-free biosensing, as the name indicates, does not need labels to make measurements easier. Rather, it utilizes the inherent physical characteristics of the analytes (such as electrical impedance, size, charge, and dielectric permittivity) to identify their existence in a sample. The capacity of label-free biosensing techniques to detect biomolecules in small reaction volumes quickly and affordably has allowed them to advance tremendously in recent years. Moreover, they are easily integrated into lab on chip systems and enable real-time target analyte concentration monitoring (Jain *et al.*, 2008). Mahmood *et al.* (2021) reported an analytical study of the optical characteristics of gold nano particles on an optical transparent substrate. The novel label-free immunosensor platform was developed to exploit the localized surface plasmon resonance phenomenon, employing a gold nanosphere probe. Integrating with anti-dengue antibody. The evaluations reveal the detection of dengue NS1 antigen concentration as low as 0.07 ± 0.01 µg/mL, Fig. 4., which increases its ability in plasmonic sensing (Mahmood *et al.*, 2021).

The surface plasmon resonance devices have wide applicability in monitoring and detecting the progress of diseases as they detect the change in the refractive index of the dielectric constant near to metal layer. Omar *et al.* developed an optical sensor based on SPR as an ailment for the diagnosis of the dengue virus. The gold/Fe-MPA-NCC-CTAB/EDC-NHS thin film was prepared, and the E-protein was detected employing the surface plasmon resonance measurement when the antigen was immobilized with complex film. The evaluation reveals the linear relationship of the SPR angle of E protein with 39.96/nM Fig. 5. So, it can be concluded that the presence bound DENV E- proteins into the IgM surface (Omar *et al.*, 2018).

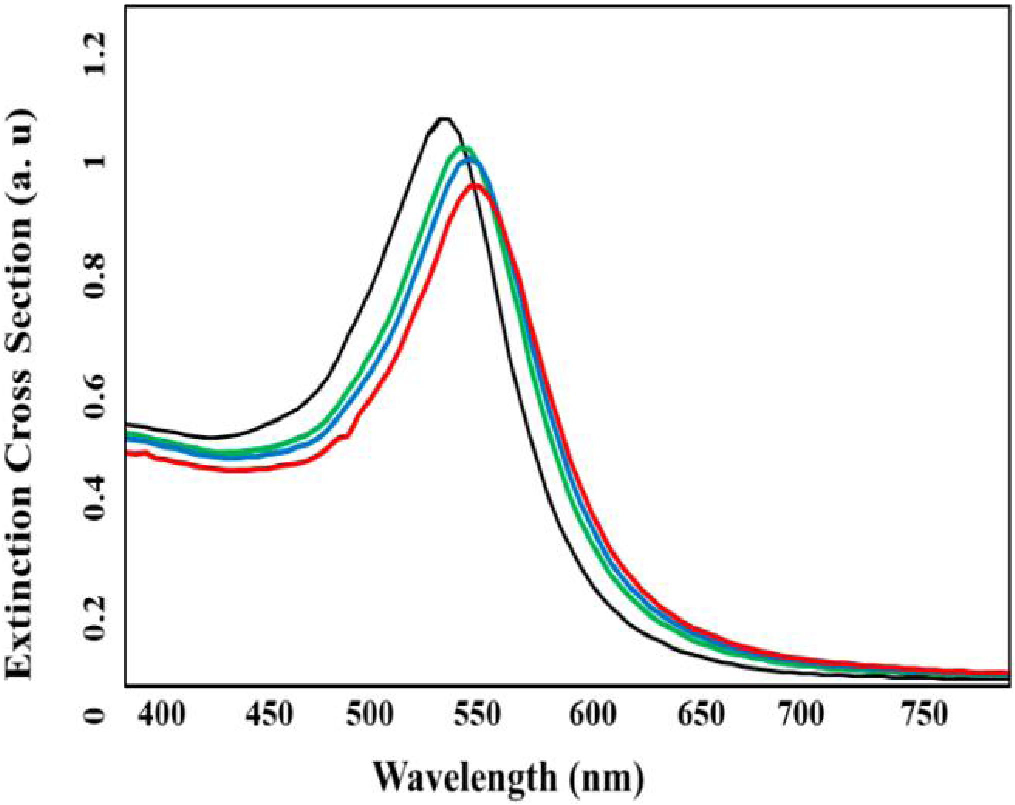

Figure 4. Colloidal Au nanosphere suspension allows for label-free biosensing of anti-NS1 antibody to NS1 antigen. The black curve represents AuNP, the green curve represents Au-Cysteamine, the blue curve represents Au-Cysteamine-Antibodies, and the red curve represents antigen detection. Adapted from (Mahmood *et al.,* 2021) under Creative Commons Attribution (CC BY-4.0) license).

10. APPLICATION OF WEARABLE SENSORS IN MONITORING VARIOUS ASPECTS OF HEALTH

Wearable sensors are cutting-edge health monitoring tools that enable continuous measurement of biological and physical characteristics. A variety of wearable devices like smartwatches, gloves, and patches are currently available with sensors that can monitor blood pressure, temperature, glucose level, and other health indicators (Kaur *et al.*, 2023) (fig. 6). Wearable and flexible technologies have been created recently to allow real-time health status monitoring, which can help offset some of the drawbacks of centralized healthcare systems. Researchers have focused a lot of interest on using wearable sensors to identify biomarkers in different body fluids. Wearable sensors are suitable for tracking a person's health or fitness without interfering with their regular activities since they are becoming increasingly more comfortable and inconspicuous. By putting the sensors in various places on the body, they may measure a variety of physiological signals and characteristics in addition to an individual's mobility and activity. The ECG, PPG, GSR, and temperature sensor are four sensors that may be used to measure and monitor, several critical physiological parameters. While a temperature sensor and a GSR monitor body temperature and skin conductivity, respectively, an ECG sensor measures the ECG signal, HR, and HRV. When determining the arterial oxygen saturation (SpO_2) level, the PPG signal is often utilized (Buxi *et al.*, 2015; Zheng *et al.*, 2014). Recent advancements in low-power wearables, affordable computing devices, and communication technologies enable the development of inconspicuous, long-term health monitoring systems (Kim *et al.*, 2019).

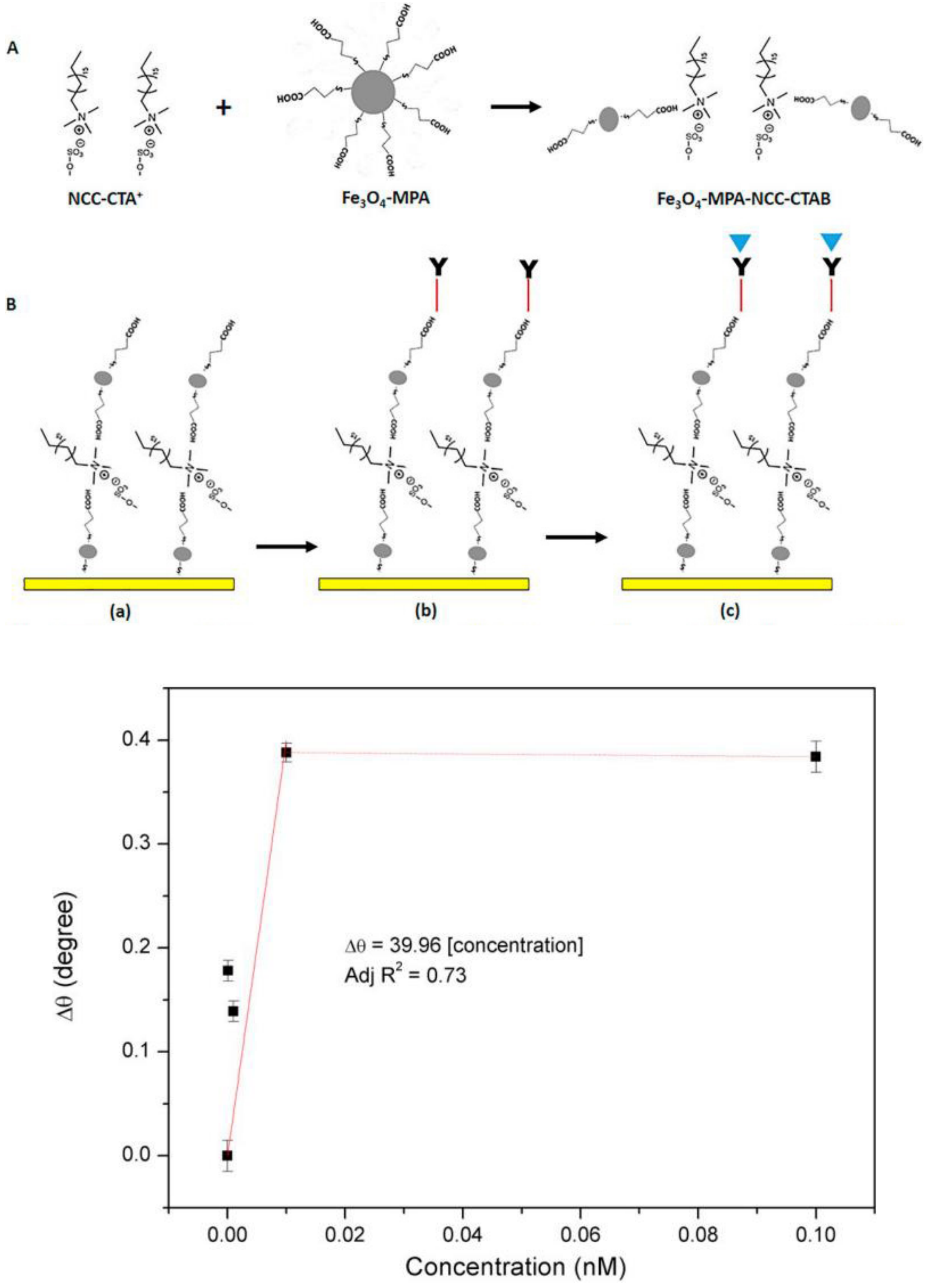

Figure 5. Fabrication of Au NMs complex (A): mechanism of preparation of composite using spin coating (B): sensor functionalization; (B-a) surface activation (B-b) immobilization of IgM antibody via a cross-linker (B-c) Injection of DENV E-protein B. The graphical representation of Change in SPR angle versus DNEV E-protein concentration. Adapted from (Omar *et al.*, 2018) under Creative Commons CC-BY license)

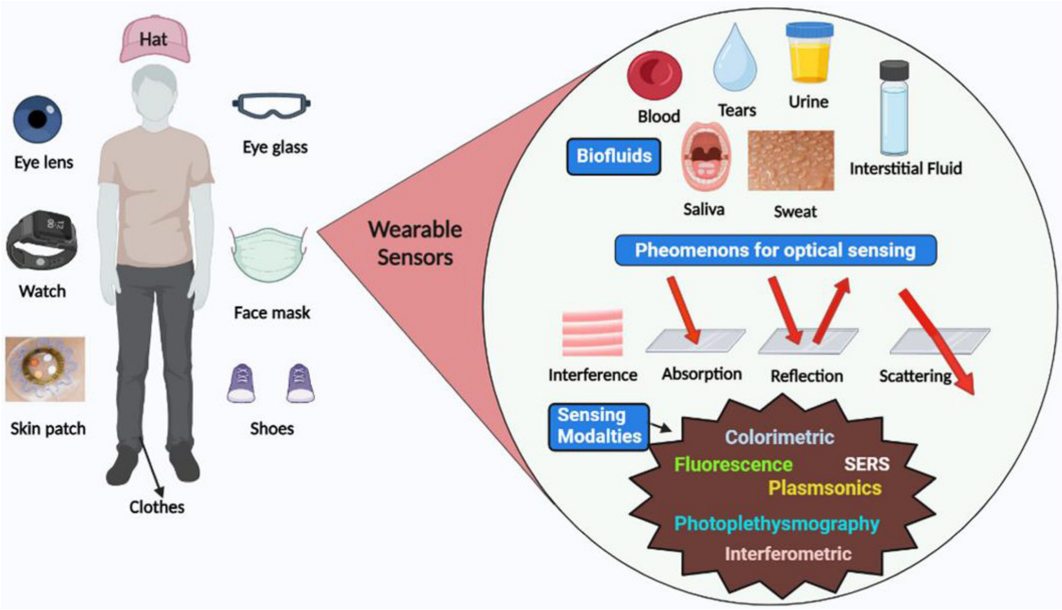

Figure 6. The available wearable optical sensors, sensing mechanisms, and biofluids for detection. Adapted from (Kaur *et al.*, 2023) under Creative Commons Attribution (CC BY) license)

11. SAFETY REQUIREMENTS OF CHEMICAL, BIOLOGICAL, AND WEARABLE BIOSENSORS

The International Organization for Standardization (ISO) provides guidelines and standards for various aspects of healthcare technology, including the safety and performance requirements of medical devices, which can apply to chemical biosensors used in healthcare settings. While there is not a specific ISO standard exclusively for chemical biosensors, several existing ISO standards cover aspects related to their safety and performance.

ISO 13485: This standard specifies requirements for a quality management system specifically for organizations involved in the design, development, production, installation, and servicing of medical devices. Compliance with ISO 13485 ensures that manufacturers adhere to strict quality control measures to maintain the safety and efficacy of medical devices, including chemical biosensors.

ISO 14971: Outlines a risk management process for medical device manufacturers to identify, evaluate, and mitigate risks associated with their products throughout the product lifecycle. Manufacturers of chemical bio-sensors must conduct thorough risk assessments to identify potential hazards and implement appropriate risk control measures to ensure patient safety.

ISO 15197: While specifically focused on blood-glucose monitoring systems for diabetes management, ISO 15197 provides valuable guidance on the performance requirements, accuracy, and usability of in vitro diagnostic test systems, including biosensors. Compliance with this standard ensures that biosensors used for glucose mon-itoring meet stringent performance criteria and provide accurate results for patient self-testing.

ISO 18113: This standard specifies requirements for the information provided by manufacturers of in vitro diagnostic medical devices, including biosensors. It ensures that the labeling of biosensors contains clear and comprehensive instructions for use, warnings, and precautions to ensure safe and effective use by healthcare professionals and patients.

ISO 23640: Although focused on liquid biopsy-based diagnostic tests, ISO 23640 outlines requirements for the analytical phase of in vitro diagnostic test systems, which can be relevant to chemical biosensors. It covers aspects such as analytical performance, sensitivity, specificity, and interference testing, ensuring the reliability and accuracy of test results.

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Compliance with these ISO guidelines and standards helps ensure the safety, performance, and quality of chemical biosensors used in healthcare applications. Manufacturers and healthcare professionals should be familiar with these standards and integrate their requirements into the design, development, validation, and use of chemical biosensors to mitigate risks and enhance patient safety.

12. CHALLENGES AND FUTURE PROSPECTIVE

The demand for nanotechnology-based devices that are convenient, sensitive, and affordable is on the rise. There is a need for more innovation to enhance the speed and accuracy of diagnostic point-of-care devices. These advancements hold great promise in biomedical applications, spanning from early disease detection to personalized treatment. Nanotechnology allows us to monitor cellular components in real-time, such as single cells or small molecules, which can lead to new insights and treatments for diseases. The tiny size of cellular components allows for the creation of nanoprobe sensors, capable of detecting biomolecules with high sensitivity, whether they're enzymes or disease markers. Miniaturized and biocompatible devices that offer non-invasive and rapid detection represent the future of disease diagnosis and prevention. Integration of drugs and fluorophores into NPs presents opportunities for both treatment and imaging purposes. Sensing biomolecules like DNA, proteins, ions, and small molecules early on can revolutionize disease diagnosis, drug development, and personalized medicine. Wearable nano-sensor devices and personalized medicine are becoming increasingly popular trends. Nanotechnology-driven medical advancements hold immense potential in reshaping the healthcare landscape. There's vast room for improvement in nanotechnology platforms for detecting signals efficiently using various NPs. Directed drug delivery via NPs offers significant advantages, including fewer side effects. Molecular nanotechnology represents a cutting-edge field that promises to deepen our understanding of emerging infectious diseases. Addressing these issues and consideration in senior design is critical to their widespread acceptance in biomedical and environmental applications. By simplifying sample preparation, identifying optimal sensor materials, and incorporating automation, these sensors have the potential to revolutionize illness diagnosis, monitoring, and environmental management (Huang *et al.*, 2021; Marzocchi & Revsbech, 2022).

13. CONCLUSIONS

Chemical and biological sensors play a pivotal role in modern health monitoring systems. Non-interventional chemical sensors and biosensors are particularly noteworthy for their ability to detect specific compounds without altering the environment. In the realm of health monitoring, these sensors are indispensable, offering real-time data on various health parameters. For instance, the detection of COVID-19 using kits involves a biological sensor that identifies viral components. The mechanism behind the reaction often utilizes antibodies that bind specifi-cally to the virus, triggering a measurable response. Graphical illustrations can vividly depict these intricate processes. Nanotechnology has revolutionized sensor fabrication, giving rise to smart biosensors with enhanced sensitivity and selectivity. NMs, such as gold or silver nanowires, play a crucial role in the development of in-telligent biosensors. These materials enable the fabrication of wearable sensors, like smartwatches, which monitor vital signs such as heart rate and oxygen levels. The incorporation of nanotechnology enhances the performance and durability of these wearable biosensors. Ensuring the safety of chemical, biological, and wearable biosensors is paramount. Rigorous safety requirements are essential to guarantee the reliability and non-toxic nature of these devices in various applications. In conclusion, the synergy of chemical and biological sensors with nanotech-nology has propelled the field of health monitoring to new heights. Wearable sensors, empowered by NMs, offer unprecedented convenience and accuracy in tracking health parameters. The continuous advancements in sensor technology not only contribute to early disease detection but also enhance overall healthcare management. As we navigate this era of smart healthcare, the integration of nanotechnology and safety protocols will remain pivotal for the success and widespread adoption of these innovative sensing technologies.

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Author Contributions

Conceptualization: PM and SS.; methodology: SM, VY, NA; formal analysis; PM and SS.; writing: SM, VY, NA, and AP; writing: review and editing, PM, AP and SM.; supervision, PM and SS.; All authors have read and agreed to the published version of the manuscript. ♦

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