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# Nanosensors as diagnostic tools: emerging concepts, opportunities, and design barriers

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Nanosensors have become a revolutionary tool, enabling early diagnosis and continuous monitoring of diseases with high accuracy. These tiny devices, operating at the nanoscale (typically between 1 and 100 nm), serve as signal generators to detect minute changes that traditional diagnostic tools might miss. The combination of nanoscale precision and their multifunctional capabilities shows a substantial advancement in nanotechnology and its practical applications. Nanotechnology is increasingly used across various fields, including healthcare, environmental monitoring, and manufacturing. However, significant challenges persist in the design and fabrication of nanosensors, particularly in achieving high precision, sensitivity, and selectivity, as well as in managing the inherent complexities of operation at atomic and molecular scales. To address these challenges, this paper explores various fabrication techniques, advances in material development, and strategies to enhance sensor feedback and responsiveness through a comprehensive knowledge system, known as the function-context-behavior-principle-state-structure (FCBPSS) framework. This framework is employed to categorize information and insights related to nanosensor development for early disease detection. One contribution of this paper is to critically examine the functions and principles that drive the development of nanosensors in biomedical systems, as well as their behavior and structural performance. Another contribution is documenting recent advancements in nanosensor fabrication, design, and materials towards future research and development in this field.

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## 1. Introduction

Nanotechnology is one of the most transformative fields in modern science, tracing its conceptual origin to Richard Feynman's 1959 lecture, *"There's Plenty of Room at the Bottom"*, presented at the annual meeting of the American Physical Society in California. This pioneering idea marked the beginning of nanoscale thinking that continues to shape today's technological innovations.[1–4] His ideas laid the foundation for future research in this field.[1] Since its inception, nanotechnology has enabled the development of a wide range of materials and components with unique properties that cannot be achieved with conventional bulk materials.[4] These materials are used across various industries, including electronics and medicine, often demonstrating superior performance compared to other conventional materials,[5] as shown in Fig. 1. In recent years, significant research efforts have only focused on improving this technology to address various challenges in different engineering and manufacturing fields.[6–9] However, nanotechnology has a broad range of applications because it enables the manipulation of matter at the atomic or molecular scale, typically ranging from 1 to 100 nm. At this nanoscopic scale, materials can exhibit behaviors and characteristics that differ significantly from those observed in conventional bulk materials.[7–10] This difference is due to several factors, including increased surface area, quantum effects, and variations in electrical and thermal conductivity, optical properties, magnetic properties, self-assembly, and self-healing abilities.[10,11]

In terms of material usage, advanced materials used in nanosensors, including carbon nanomaterials, metal nanomaterials, metal oxide nanomaterials, ceramic nanomaterials, nanocomposites, and organic nanomaterials, play a crucial role in nanotechnology.[10] These materials exhibit unique properties at the nanoscale, making them highly useful for various applications.[12] These materials are often designed to leverage special characteristics that emerge at the atomic or molecular level, resulting in enhanced mechanical strength, electrical conductivity, chemical

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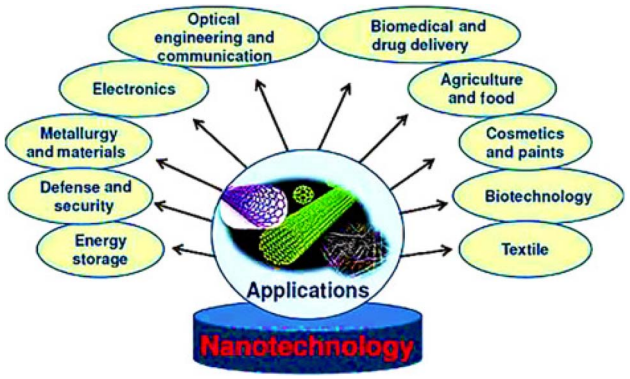


Fig. 1 Different applications of nanotechnology, reproduced from ref. 12 with permission from Elsevier, copyright 2019.

reactivity, or light absorption.[11] Nanotechnology applications capitalize on these unique properties, enabling the production of a diverse range of components across multiple fields.[11,12] Nanotechnology has a wide range of applications across various domains. In the field of medicine, it is used for targeted drug delivery and advanced diagnostics. In environmental engineering, it plays a vital role in pollutant remediation and water purification.[13–16] Additionally, nanotechnology contributes to high-efficiency energy storage and solar technologies.

In electronics, it enables the development of miniaturized and high-performance devices. It also leads to the creation of smart materials and nanocomposites.[14–16] Furthermore, nanotechnology is making significant strides in food and agriculture, offering innovative solutions and enhancing cosmetic formulations. Lastly, it provides emerging tools for defense and security applications.

Nanotechnology materials have unique physical, chemical, electrical, and optical properties. These include nanowires, nanotubes, quantum dots, nanoparticles, nanorobots, nanoelectronics, and nanofibers, among others (as shown in Fig. 2). Nanotechnology finds various uses in medicine, electronics, nanosensors, energy, and materials science.[17] Of these, nanosensors are especially important as a key sensing technology. They are designed to detect and measure physical, chemical, or biological features at the nanoscale, typically ranging from 1 to 100 nanometers. Nanosensors leverage the unique properties of materials at this scale, including high surface area, quantum effects, and enhanced sensitivity.[18–21] They can sense tiny environmental changes and are used in many fields, from medical diagnostics to environmental monitoring.

Several review papers have explored nanosensors and nanobiosensors used in biomedical diagnostics.[22–28] These include recent surveys on nano-engineered sensor systems for disease detection, nanotechnology-enabled biosensors for point-of-care testing, and nanomaterial-based sensing platforms. These reviews have provided valuable insights into applications such as cancer biomarker detection, infectious disease diagnostics, personalized healthcare monitoring, and point-of-care technologies.[22–26] However, they tend to address nanosensors extensively and do not specifically synthesize the field in terms of emerging design concepts, translational opportunities, and persistent design barriers to clinical deployment.

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The widespread use of nanosensors faces significant challenges that require innovative solutions in design, performance optimization, and application-specific development. Yeo *et al.*[18] discussed various challenges related to the use of nanosensors in healthcare systems. These challenges include biocompatibility issues, long-term stability in biological environments, immune reactions, and potential sensor degradation. Han *et al.*[19] also provided a comprehensive analysis of nanosensors for structural health monitoring (SHM). Their work highlighted challenges related to deploying nanosensors, such as signal processing, power supply, calibration, sensor reliability, environmental factors, durability, and data interpretation. A significant challenge in using the electrospinning process to produce 3D nanofibers is achieving a uniform fiber diameter, which is crucial for creating nanowires suitable for sensor applications. The defect rate, which encompasses issues such as pore formation and bead creation, can be quite high if the operational setup is not properly managed.[20] Additionally, antibody-based biosensors (immunosensors) may encounter issues with cross-reactivity, where unrelated targets with similar antigenic structures can lead to false positive signals, potentially affecting the stability and reproducibility of the biosensors.[21] Another challenge facing the use of nanosensors in biomedical applications is the selectivity and sensitivity of the sensors, especially for complex biological samples or trace chemicals.[6–9]

This review examines the functionality of nanosensors in biomedical applications and highlights the key challenges that influence their performance. It proposes potential solutions

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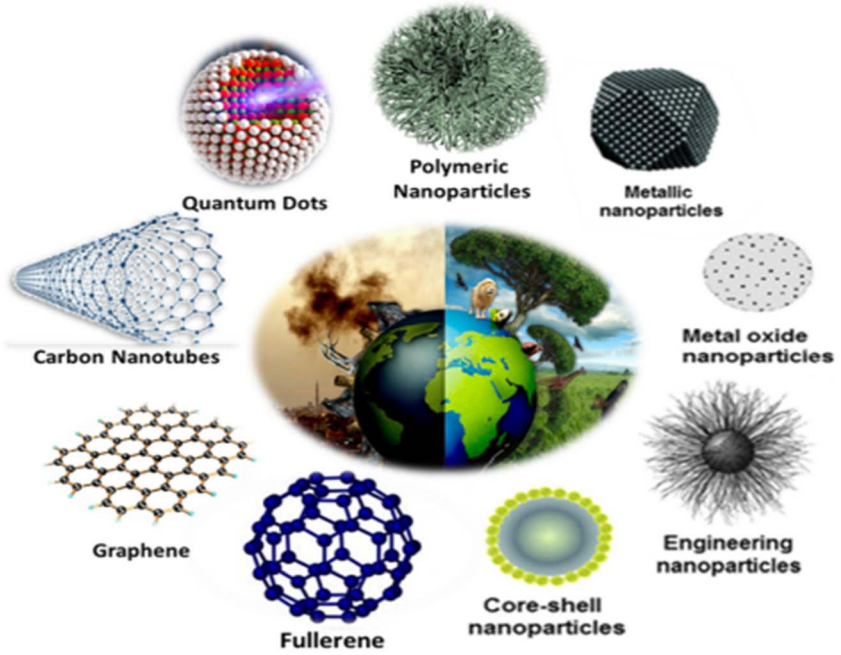


Fig. 2 An overview of nanotechnology components, reproduced from ref. 11 with permission from Elsevier, copyright 2023.[11,12]

during the design phase and towards advancements in material innovation, fabrication techniques, and sensor multi-functionalization. The main goal of this paper is to enhance the design and development of nanosensors and promote their use as reliable diagnostic tools for the early detection of diseases in biomedical settings.

The FCBPSS framework is used in this work to systematically guide design, optimization, and functional prediction. The

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framework systematically links function, context, behavior, principle, structure, and state, enabling researchers to identify cause-effect relationships and design levers that directly influence performance. For instance, understanding how a particular nanostructure (structure) under specific environmental conditions (state) affects the signal transduction (behavior) allows engineers to iteratively optimize sensitivity and selectivity. This integration of mechanistic behavior, functional mapping, and design logic produces actionable insights that inform device fabrication, material selection, and operational strategies, transforming conceptual understanding into practical, high-performing nanosensor solutions.[29–32] The FCBPSS helps ensure that all aspects of the system are considered, providing a comprehensive understanding of its components and their relationships. In practice, applying the FCBPSS framework can enhance the analysis and development of various systems, including complex technologies like nanosensors. By structuring information within these categories,[33,34] researchers, scientists, and engineers can uncover new insights, enhance decision-making processes, and foster innovation by recognizing and leveraging the interconnections among the various elements of the system.

## 2. Materials and methods

The criteria for selecting articles in this review included several significant factors relevant to the topic and practical applicability to current challenges in nanosensor development. We prioritized articles published from 2020 to 2025 to ensure the inclusion of the latest research and advancements in materials development. Emphasis was placed on studies published in reputable journals and conferences that had undergone stringent peer-review processes. Additionally, we preferred studies that utilized strong methodologies, included experimental validation, and presented credible data. The selection process aimed to encompass a diverse range of authors, institutions, and geographic areas, offering a comprehensive view of the research landscape. The criteria for exclusion primarily centered around the timing of publication and accessibility.

This section describes the methodology used for reviewing the nanosensor fabrication process, which is systematically organized around six key design frameworks: Function, Context, Behavior, Principle, State, and Structure (FCBPSS).[35–50] These principles form the foundation of the nanosensor design framework, guiding the development of highly sensitive and application-specific nanosensors. By applying the FCBPSS model, we identify and analyze the critical methodological factors that impact the performance and feasibility of nanosensors. This integrated approach enables a comprehensive evaluation of both the technical and operational aspects of nanosensor design, encompassing material selection, signal transduction mechanisms, environmental adaptability, and long-term stability.

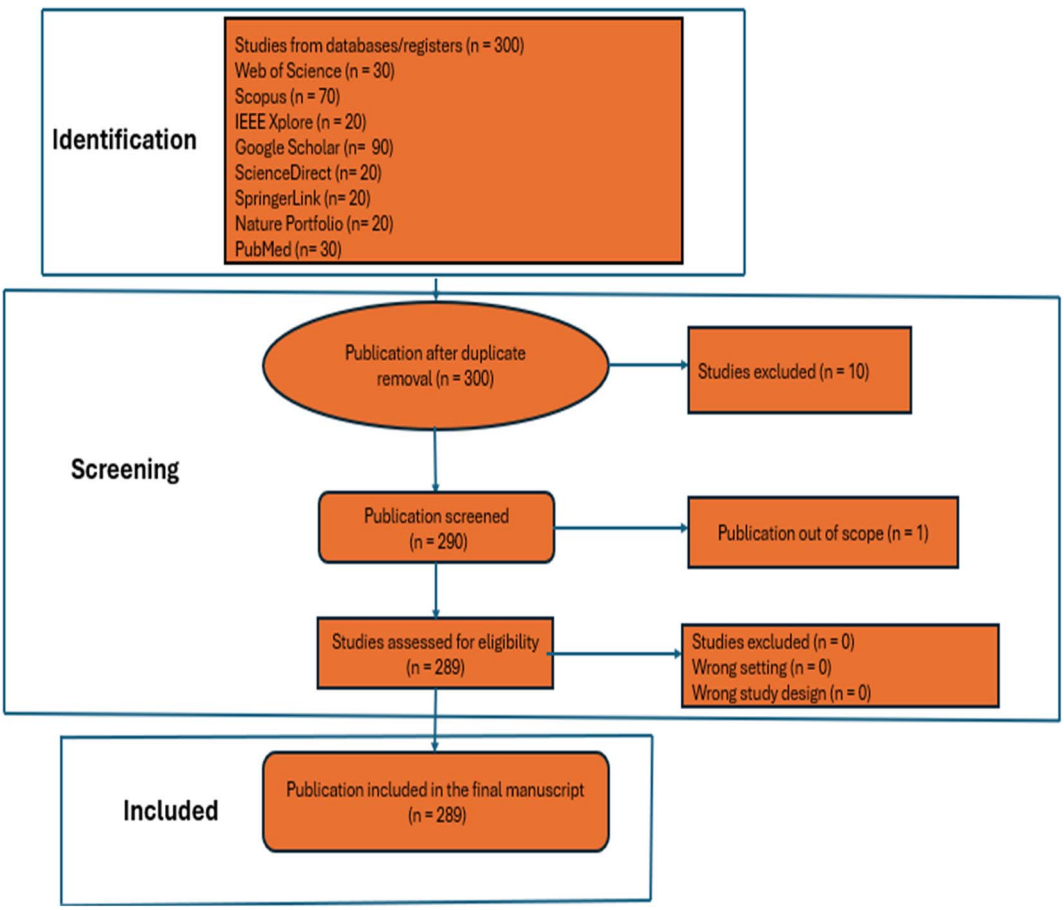


Fig. 3 Information flows across the different stages of a systematic review process.

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Table 1 Keywords and databases used for literature search

| Keyword category | Keywords used |
|---|---|
| General nanosensor terms | "Nanosensor", "nanomaterials", "nano-enabled sensors", "nanodevices", "nano-biosensors", "nano-based detection" |
| Target properties | "Analyte", "sensitivity", "selectivity", "specificity", "detection limit", "response time", "reproducibility", "sensor drift", "stability" |
| Fabrication & materials | "Fabrication methods", "nanofabrication", "synthesis techniques", "surface modification", "surface functionalization", "manufacturing of nanosensors" |
| Advanced design concepts | "Multi-functionalization", "miniaturization", "smart materials", "hybrid nanosensors", "self-assembled nanosensors", "biocompatible nanomaterials" |
| Framework and methodology | "FCBPSS", "function-based sensor design", "sensor architecture", "design principles in nanosensors", "system-level nanosensor design" |
| Challenges and limitations | "Nanosensor challenges", "environmental interference", "biofouling", "sensor degradation", "design issues in biosensors", "limitations in nanosensor applications" |
| Application areas | "Environmental monitoring", "biomedical sensing", "point-of-care diagnostics", "therapeutic monitoring", "agricultural sensors", "industrial nanosensors" |
| Research and trends | "Trends in nanosensor research", "emerging nanosensor technologies", "recent advances in nanosensors", "future of nanosensors", "nanosensor development trends" |
| Security and ethics | "Data security in nanosensing", "nanoethics", "privacy in biosensing", "toxicity of nanomaterials", "environmental impact of nanosensors" |
| Databases used | "Google scholar", "Scopus", "Web of Science", "Nature", "ScienceDirect" |

Additionally, we reviewed recent empirical research focused on advancements in nanosensors as medical diagnostic tools. To compile the relevant literature, we employed a systematic review approach,[43–45] as outlined in Fig. 3. Searches were conducted across several major databases, Google Scholar, Scopus, Web of Science, PubMed, ScienceDirect, IEEE Xplore, SpringerLink, and Nature Portfolio, due to their broad publication coverage and global accessibility. Using the keywords outlined in Table 1 and with reference to the citation coverage detailed in Table 2, the initial search yielded 90 articles from Google Scholar, 70 from Scopus, 30 from Web of Science, 30 from PubMed, 20 from ScienceDirect, 20 from IEEE Xplore, 20 from SpringerLink, and 20 from Nature Portfolio. After eliminating duplicate records, the total number of articles stood at 300. However, 10 articles were not

Table 2 Citation coverage summary for nanosensors as diagnostic tools

| Database | Citation count (%) | Key observations |
|---|---|---|
| Google Scholar | ~80–70% of all citations | Highest citation coverage. Includes peer-reviewed articles, theses, books, and conference papers. Broadest in scope, but less selective |
| Scopus | ~60% of all citations | Good multidisciplinary coverage. Includes more engineering and applied science journals than WoS. Strong filtering and indexing quality |
| Web of science | ~52% of all citations | Most selective and curated. Focuses on high-impact journals. Coverage varies significantly across disciplines |
| PubMed | ~45–60% (biomedicine-focused) | Specialized in biomedical literature. Excellent for nanosensors used in diagnostics, especially in clinical and health-related applications |
| ScienceDirect | ~40–50% (Elsevier journals) | Covers Elsevier journals in science and engineering. Often used for accessing full-text materials and research in sensor technology |
| IEEE Xplore | ~35–45% (engineering focus) | Excellent source for nanosensor integration with electronics, IoT, and embedded systems. Strong in technical conference proceedings |
| SpringerLink | ~30–40% | Good coverage in applied sciences and nanotechnology. Offers access to multidisciplinary journals and books |
| Nature Portfolio | ~25–35% | Highly selective. Publishes cutting-edge, high-impact research. Useful for referencing state-of-the-art nanosensor breakthroughs |

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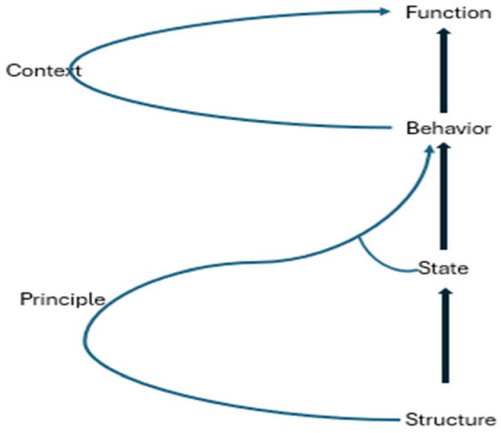


Fig. 4 FCBPSS model, reproduced from ref. 30 with permission from Elsevier, copyright 2004.

accessible, leaving 290 for further evaluation. Following a review of titles and abstracts, 1 article was excluded because it was either not published in english or was unrelated to nanosensor applications in diagnostic systems. This process resulted in a final selection of 289 articles that met our inclusion criteria, which focused on nanosensor development for diagnostic purposes, design challenges in environmental and physical contexts, fabrication limitations, and research considerations relevant to design methodologies. The step-by-step process of identification, screening, eligibility assessment, and inclusion is illustrated in Fig. 3, which provides a clear overview of our methodical approach and the current landscape of research in this rapidly evolving field.

### 2.1 Research question procedure for developing a nanosensor

The research question was developed using the FCBPSS framework (see Fig. 4), which includes six key design principles for nanosensor development: function, context, behavior, principle, state, and structure. The research question was developed to explore the role of nanosensors in biomedical diagnostics while addressing major challenges that hinder their effectiveness and performance. Additionally, it offers research considerations and suggests solutions to these challenges during the design phase, focusing on advances in materials, fabrication techniques, and multi-functionalization. The research questions are listed below.

- Function: What specific biomedical functions can nanosensors effectively perform, and how do these functions influence their design parameters?
- Context: In what biomedical environments (*e.g.*, blood, saliva, interstitial fluid) are nanosensors most challenged, and how does the surrounding context affect their performance and stability?
- Behavior: How do nanosensors behave under variable physiological and environmental conditions, and what mechanisms can enhance their reliability in real-time diagnostics?
- Principle: What fundamental sensing principles (*e.g.*, electrochemical, optical, piezoelectric) are most suitable for biomedical nanosensors, and how do these influence design trade-offs such as sensitivity *versus* selectivity?
- State: How do the material and operational states (*e.g.*, stability, degradation, response time) of nanosensors evolve during their lifecycle, and what design interventions can maintain or restore optimal function?
- Structure: How do structural configurations such as nanomaterial type, surface modification, fabrication technique (for example, 3D printing), and multi-functionalization impact the performance of nanosensors in biomedical diagnostics, and how can these be optimized during the design phase?

### 2.2 Development of nanosensors using the FCBPSS framework approach

The FCBPSS framework is particularly useful for designing and developing nanosensors. This framework provides a structured

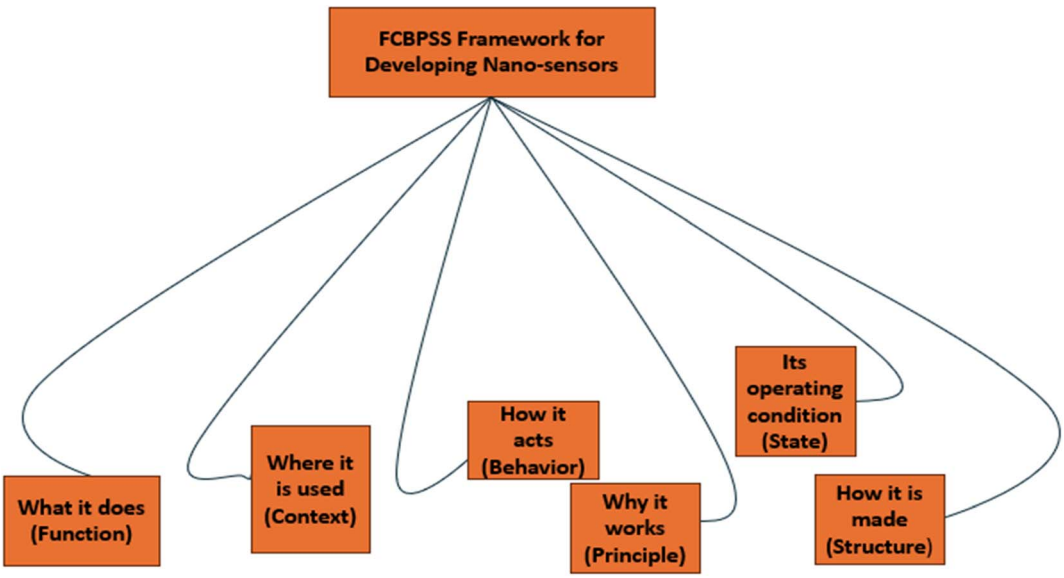


Fig. 5 The FCBPSS framework outlines six key design principles for nanosensor development.

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Table 3 FCBPSS framework for developing nanosensors

| FCBPSS framework system for nano-sensors | Question | Conditions | Applications |
|---|---|---|---|
| Function | What is the nanosensor designed to do? | • Detect and measure specific analytes (*e.g.*, glucose, toxins, gases, pathogens) with high sensitivity and specificity<br>• Convert a physical or chemical interaction into a quantifiable signal (electrical, optical, thermal, *etc.*)<br>• Often includes real-time or continuous monitoring capability | A nano-biosensor can be designed to detect glucose in diabetic patients |
| Context | Where and under what conditions does the nano-sensor operate? | • Environmental conditions: temperature, pH, humidity, presence of interfering substances<br>• Application setting: medical diagnostics (*in vivo*, wearable), industrial gas leak detection, agricultural soil analysis<br>• User/system interface: standalone, wearable, or part of a larger IoT system | A wearable nanosensor used in a hospital can be designed under certain conditions to monitor blood oxygen levels in real-time |
| Behavior | How does the nano-sensor perform its function over time? | • Responds to changes in analyte concentration by altering a measurable property<br>• May exhibit dynamic behaviors such as signal drift, sensitivity decay, or threshold triggering<br>• Can include feedback mechanisms (*e.g.*, alert generation, activation of actuators) | The electrical resistance of a carbon nanotube-based gas sensor decreases over time as it detects increasing gas concentrations |
| Principle | What is the scientific basis or phenomenon behind the sensor's operation? | • Electrochemical: change in voltage or current (*e.g.*, amperometric glucose sensors)<br>• Optical: light absorption, fluorescence, surface plasmon resonance (*e.g.*, gold nanoparticle sensors)<br>• Mechanical: mass change or vibration shift (*e.g.*, nano-cantilevers)<br>• Magnetic: magnetoresistance or nanoparticle tagging | Quantum dots exhibit size-dependent fluorescence, which is used to detect specific biomolecules |
| State | What are the internal conditions or modes of the nanosensor at a given time? | • Idle: waiting for input<br>• Active: detecting and transducing a signal<br>• Processing: analyzing and transmitting the signal<br>• Error/Fault: malfunction or drift due to damage or environmental interference | A biosensor is in a "calibration state" before being deployed for accurate measurement |
| Structure | What is the physical and material composition of the nanosensor? | • Composed of nanomaterials like carbon nanotubes, graphene, quantum dots, and metal nanoparticles<br>• Structure may include functional layers (receptors, enzymes, polymers), substrates, transducers, and electronic circuits<br>• Designed for integration with wearable devices, microfluidic systems, or wireless transmitters | A multilayer nanosensor consisting of a graphene sheet functionalized with antibodies on a silicon substrate |

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method for integrating design, mechanisms, and functionality. By clearly connecting function (the detection capabilities of the nanosensor) with behavior (its responsive actions to external stimuli) and principle (the foundational sensing mechanism, such as electrochemical or optical transduction), researchers can ensure reliable sensor performance in specific environments. Additionally, aligning structure (nanomaterials and device design) with state (operational conditions and environmental influences) allows for predictive modeling and optimization, helping to bridge the gap between theoretical design and real-world application. This comprehensive approach promotes a deeper understanding of mechanisms, functional mapping, and logical design, which are essential for creating highly sensitive, selective, and durable nanosensing devices.

The FCBPSS is a crucial conceptual framework for developing any functional system, originally proposed by Zhang and Lin[46–48] and subsequently extended by Zhang and Wang.[49] This system

Table 4 Applications of nanosensors in biomedical systems

| Application area | Recent research | Key findings | Ref. |
|---|---|---|---|
| Cancer detection | This work developed a nano-sensor utilizing metastasis-initiating stem cells to detect lung cancer with high sensitivity and specificity | Achieved 100% sensitivity and 88% specificity in detecting lung cancer from a 5 μL blood sample using a machine learning model | 65 |
| Pathogen detection | This study reviewed advancements in nano-sensors for detecting hospital-associated pathogens | Highlighted the development of nano-biosensors for detecting bacteria, fungi, and viruses in hospital environments, emphasizing the need for rapid and sensitive detection methods | 66 |
| Flexible and Biodegradable sensors | This examined implantable chemical sensors that use flexible and biodegradable materials | Examined how these sensors can enable real-time monitoring of biomarkers like metabolites and neurotransmitters, providing valuable insights for clinical applications | 67 |
| Oral health diagnostics | Recent advancements in nano-biosensors for periodontitis detection | This paper emphasized the role of nanosensors for periodontitis detection, enabling timely diagnosis and precise drug delivery | 68 |
| Health-monitoring biomarkers | Recent advances in graphene-based nano-biosensors for salivary biomarker detection | This article examines the progress of graphene-based nano-biosensors specifically designed to detect salivary biomarkers. It explores the structural designs of graphene electronics, their role in health monitoring, and the challenges, along with prospects for clinical point-of-care applications | 69 |
| Bladder cancer theragnostic | This paper reviewed nanomaterial-based biosensors and theranostic nanomedicine for bladder cancer | This paper explored the use of nanomaterials in the diagnosis and therapy of bladder cancer, including biosensors for urine biomarkers and nanocarriers for targeted drug delivery | 70 |
| Personalized healthcare | Recent review on the application of nanosensors in personalized healthcare | Their findings indicated that implementing nano-sensors in healthcare can enhance disease diagnosis accuracy (ADD) by 35% and elevate personal health monitoring (PHM) quality by 23%. Additionally, this technology has decreased the diagnostic response time (DRT) by 21% | 71 |
| Cancer detection | Leveraging nanomaterials for ultrasensitive biosensors in early cancer detection | Cancer biomarkers, which are detectable in body fluids, provide valuable diagnostic information. Moreover, recent advances in nanotechnology have resulted in the development of highly sensitive nano-biosensors | 72 |


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comprises six conceptual architectures:[49] structure, state, behavior, principle, context, and function (see Fig. 4). The system's structure defines its components and their arrangement, its state represents the current conditions, its behavior describes how it acts over time, its principle explains the underlying rules governing it, its context includes the external environment influencing it, and its function specifies the purpose it serves. This study employs the FCBPSS framework to guide the understanding and design of nanosensors, specifically addressing the research question outlined in Section 2.1 and supported by the information presented in Fig. 5 and Table 3.

## 3. Functional roles of nanosensors in biomedical systems

According to Table 4, nanosensors have emerged as valuable tools for detecting and monitoring diseases, such as cancer and infectious diseases, at earlier stages.[21] These devices provide more precise and real-time data, helping to prevent complications and improve overall patient management.[21,50] These sensors have been effectively used in a range of biomedical applications, including Cancer Biomarkers, Infectious Diseases, Monitoring biomarkers for diabetes (*e.g.*, glucose, insulin levels), kidney dysfunction (*e.g.*, creatinine, urea), or cardiovascular risk factors (*e.g.*, cholesterol, troponin), detecting neurodegenerative disease biomarkers such as amyloid-β or tau proteins in Alzheimer's disease and this sensor is most beneficial where early, rapid, and highly sensitive detection can dramatically improve patient outcomes, especially in cancer, infectious diseases, and metabolic disorder.[51–58] The nanosensor efficacy includes early disease detection (as provided in Fig. 6), point-of-care diagnostics, targeted drug delivery, continuous health monitoring, *in vivo* monitoring and imaging, antibacterial and antiviral treatments, drug efficacy monitoring, and regenerative medicine, as well as the diagnosis of neurodegenerative diseases.[50,59–64] Fig. 6 illustrates the potential applications of nanosensors across various body regions.

### 3.1 Limitations of current diagnostic standards

Conventional diagnostic methods, such as culture-based assays, enzyme-linked immunosorbent assays (ELISA), microscopy, and polymerase chain reaction (PCR), remain indispensable in clinical practice but suffer from several critical limitations. These methods often involve lengthy processing times and complex protocols, delaying actionable results and treatment decisions.[51–54] For example, culture and microscopy can take days, and immunoassays like ELISA require extensive sample preparation and analysis

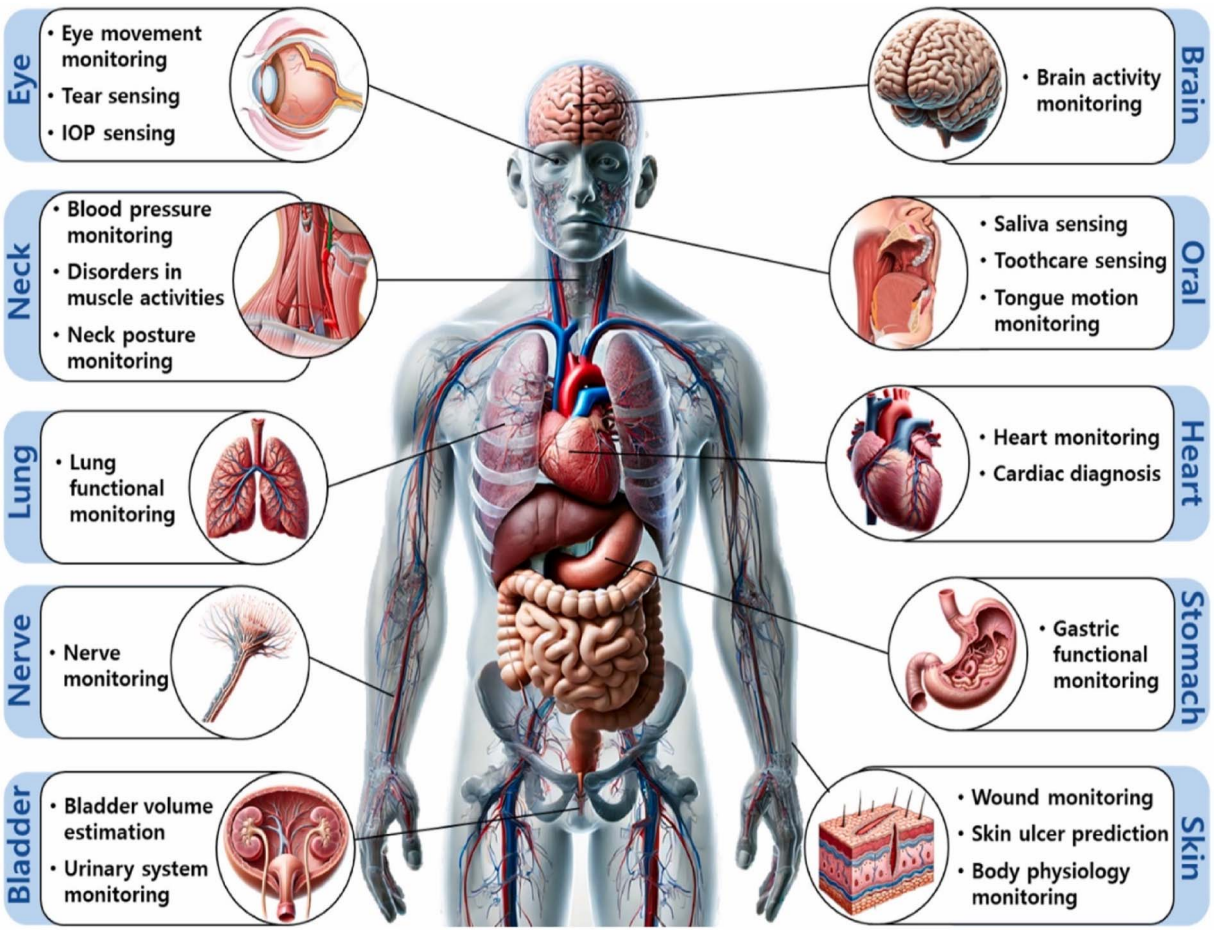


Fig. 6 Potential locations for placement of nanosensors in body organs for function monitoring and early disease detection, reproduced from ref. 63 with permission from Elsevier, copyright 2025.

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time.[53] ELISA is a widely used laboratory technique that detects and quantifies proteins, antibodies, and hormones through the use of enzyme-mediated color changes. PCR, on the other hand, is a method used to amplify specific DNA sequences, allowing for the rapid detection of genetic material from pathogens.

Sensitivity poses another issue in current diagnostic tools. Standard platforms often need high concentrations of biomarkers to generate detectable signals, which means that low-abundance biomarkers linked to the early stages of disease may go unnoticed.[54] This reduces the chances for timely intervention when the likelihood of successful treatment is at its highest. Moreover, many clinical tools do not offer real-time monitoring; diagnostics usually provide a snapshot at a single time point rather than ongoing physiological feedback.[55] This restricts healthcare providers' capacity to monitor swift biochemical changes or the progression of disease.

Additional challenges, such as cumbersome equipment, labor-intensive procedures, and reliance on specialized lab facilities, further limit accessibility, point-of-care application, and scalability. Together, these challenges highlight the pressing need for nanoscale sensing technologies that provide rapid, highly sensitive, and real-time detection of clinically significant biomarkers.[54,55]

## 4. Environmental context of the nanosensor

Nanosensors are highly sensitive devices designed to detect physical, chemical, or biological stimuli at the nanoscale, as shown in Fig. 7. The conditions and environment under which a nanosensor operates significantly affect its performance, accuracy, and longevity.[73] This section is designed to discuss the environmental context in which the nanosensor operates and performs its functions. The significant factors to discuss in this section include physical environment, chemical environment, biological environment, and operational conditions.

### 4.1 Physical environment

Nanosensors, due to their small size and high surface-area-to-volume ratio, are highly sensitive not only to target analytes but also to external physical environmental factors. In this context, nanosensors are often deployed in challenging environments that require devices to exhibit high stability and resilience.[74,75] Depending on their application, they may need to operate under varying temperatures, fluctuating humidity levels, exposure to electromagnetic fields or vibrations, mechanical stress, or movement in dynamic systems (*e.g.*, wearable sensors).[76,77]

Design issues 1: these issues include temperature fluctuations, humidity, light exposure, pressure, dust, and mechanical stress, all of which can significantly affect sensor sensitivity, stability, and longevity. Designing nanosensors for operation in physically demanding environments involves careful material selection, device architecture, packaging, and signal processing techniques to ensure stability, resilience, and sensitivity.

Research direction for design issue 1: incorporate temperature compensation circuits, thermal insulation, or materials with low thermal sensitivity. Use hydrophobic coatings, sealed packaging, or environment-specific calibration. Apply UV filters, optical shielding, or photo-stable materials. Integrate sensors into flexible substrates, employ protective encapsulation, or include mechanical damping mechanisms. Consider nanostructured filters, self-cleaning surfaces, or systems for periodic sensor maintenance and regeneration.

### 4.2 Chemical environment

The chemical environment includes the presence of gases, pH levels, or other chemical species that may interact with the sensor surface.[78–80] In a biomedical context, nanosensors may operate in blood, saliva, or interstitial fluids, requiring biocompatibility and resistance to biofouling.[78–83]

Design issues 2: developing nano-sensors for challenging chemical environments, particularly in biomedical settings (*e.g.*, blood, saliva, interstitial fluid), necessitate addressing chemical stability, selectivity, biocompatibility, and anti-biofouling properties, as outlined in Table 5. The sensor's active material must be chemically stable and selective for its target analyte. If it is too reactive or non-specific, it can interact with unintended compounds, causing false positives or inaccurate readings. A

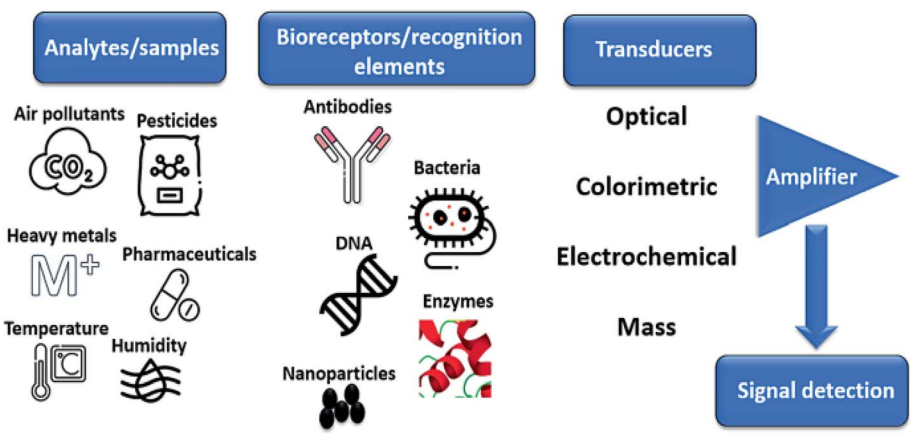


Fig. 7 Nano-sensors and nano-biosensors for monitoring environmental contaminants, reproduced from ref. 73 with permission from Springer nature, copyright 2021.

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Table 5 Key challenges in the chemical environment

| Chemical factor | Impact on nano-sensor performance | Ref. |
|---|---|---|
| Reactive gases (*e.g.*, $NO_x$, $H_2S$, CO) | Can chemically degrade or irreversibly alter the sensor surface | 78 |
| pH variability | Affects the surface charge and reactivity of nanomaterials | 79 |
| Biological fluids (blood, saliva, ISF) | Introduce proteins, enzymes, and salts that tend to biofouling and corrosion | 80 and 81 |
| Ionic strength/Salinity | Interferes with signal detection, especially for electrochemical sensors | 81 and 82 |
| Enzymatic activity | Can degrade organic components or alter recognition elements | 83 |

Table 6 Key challenges in the biological environment

| Biological factor | Challenge it presents | Ref. |
|---|---|---|
| Complex matrices | Proteins, lipids, enzymes, and salts can interfere with detection | 84 |
| Competing molecules | Structurally similar molecules may bind non-specifically | 85 |
| Biofouling | Protein or cell adhesion blocks sensing surfaces | 86 and 87 |
| Immune response | The sensor may be attacked or degraded *in vivo* | 84 and 88 |
| Fluid dynamics | Movement in blood or tissue changes the local analyte concentration | 84 |
| Cellular uptake (for intracellular sensors) | Endocytosis, lysosomal degradation | 89 |

sensor may also exhibit different behavior at various pH levels, leading to signal drift or degradation over time. Similarly, high ionic strength can screen electrostatic interactions, reducing sensitivity in charge-based detection.

Research direction for design issue 2: use surface coatings (*e.g.*, polymer layers) to enhance selectivity, functionalize with specific ligands or antibodies, incorporate anti-fouling materials to reduce biofouling or degradation, engineer materials that are buffer-insensitive or include internal calibration, embed reference electrodes or internal standards in the design, and limit operational pH range through environmental control or sample pre-treatment.

### 4.3 Environmental monitoring

In environmental monitoring, nanosensors are used to detect toxic gases and chemical contaminants.[73,74] Effective monitoring requires integrating nanosensors into wireless sensor networks or IoT platforms. Sensors (especially nanosensors) must detect low concentrations of pollutants (*e.g.*, VOCs, heavy metals, $NO_2$) with high accuracy. These applications require high selectivity to accurately identify specific contaminants in complex environmental samples, as well as strong chemical stability to maintain sensor performance over time under harsh or reactive conditions.

Design issues 3: designing a nanosensor to detect toxic gases, heavy metals, organic pollutants, or other contaminants in air, water, or soil is technically demanding. These applications demand high selectivity (distinguishing target analytes from background noise), chemical stability (resisting harsh or reactive environments), sensitivity at trace levels (ppm, ppb, or even ppt), portability for field deployment, and low power for autonomous operation.

Research direction for design issue 3: utilize nanostructured materials, such as metal–organic frameworks and doped carbon nanotubes, to improve analyte selectivity. Explore bio-recognition elements, such as aptamers and molecularly imprinted polymers, for targeted sensing. Develop multi-analyte detection strategies to monitor multiple pollutants simultaneously, study low-power data transmission methods suitable for remote monitoring, such as LoRaWAN and NB-IoT. Investigate energy harvesting techniques, such as solar power and vibration-based methods, for long-term deployments. Additionally, focus on data integrity and edge computing solutions to minimize dependency on continuous connectivity.

### 4.4 Biological environment

In biosensing applications, nanosensors must function in complex biological matrices, often with competing molecules or potential sources of interference. These environments demand high specificity to target molecules, non-invasive integration with tissues or cells, and long-term operational stability in bodily fluids or cellular environments, as discussed in Table 6.

Design issues 4: nanosensors used in biosensing, whether for diagnostics, monitoring, or therapeutic feedback, must be designed to operate in complex biological matrices, such as blood, saliva, interstitial fluid, or even within cells. These conditions introduce biochemical noise, competing molecules, and immune reactions, as well as the challenge of maintaining stable sensor function over time (see Fig. 7).

Research direction for design issue 4: developing anti-fouling coatings such as PEGylation and zwitterionic surfaces, along with self-cleaning or responsive surfaces to ensure long-term functionality. This includes functionalizing surfaces with high-affinity biorecognition elements like antibodies, aptamers, and MIPs. Additionally, molecular engineering is used to optimize recognition sites for target analytes, study material degradation kinetics in biological environments, and assess the immune compatibility and cytotoxicity of nanomaterials. Machine learning algorithms can also be employed for signal correction and noise filtering.

## 5. Mechanisms underlying nanosensor behavior

In designing a nanosensor, behavior refers to how the sensor responds to the presence of a target substance and how it

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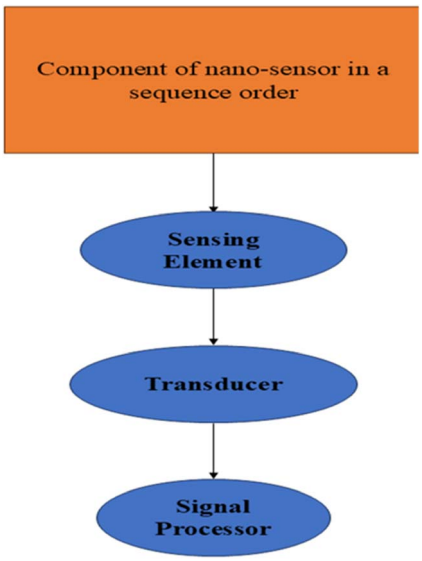


Fig. 8 Schematic representation of the basic components of a nano-sensor. A typical nanosensor consists of three fundamental elements: a recognition element, a transducer, and a signal processing unit. The recognition element selectively interacts with the target analyte, often using nanomaterials such as nanoparticles, nanotubes, or quantum dots to enhance sensitivity and specificity. The transducer converts the biochemical or physicochemical interactions into a measurable signal, which is then amplified, processed, and interpreted by the signal processing unit.

performs over time under various conditions, including its sensitivity, selectivity, response time, and stability in a real-world environment. Sensors can measure down to the level of individual molecules. They comprise four primary components: an analyte, a sensor, a transducer (which transforms one type of energy into another), and a detector. Generally, nanosensors operate by observing the electrical variations in the sensor materials. The analyte moves from the solution to the sensor's surface, where it interacts in a specific and efficient manner. This interaction alters the physicochemical properties of the transducer's surface, resulting in modifications to its optical or electronic characteristics. These alterations are then converted into an electrical signal that can be detected, as shown in Fig. 8.

Nanosensors function by interacting with nanomaterials and target analytes, resulting in measurable changes in physical or chemical properties. These alterations are transformed into signals (electrical, optical, thermal, *etc.*) that can be quantified and understood. At the nanoscale, materials exhibit unique properties, including a greater surface area, quantum effects, and enhanced reactivity. These features enable nano-sensors to detect tiny amounts of substances with exceptional sensitivity and specificity. Early disease detection remains a significant challenge in medicine.[90–93] Given the progress in infectious disease and cancer rates, efforts are required to facilitate the discovery of new diagnostic systems, such as sensors for disease detection, as well as the identification of barriers to implementing this innovative system. Procrastination diagnoses can lead to limited treatment options, increased disease progression, and, in some cases, can even result in death. These tiny sensors, which utilize nanoparticles and chemical agents, can detect and monitor physical components such as disease biomarkers at the nanoscale, offering a unique advantage that is rarely found in other diagnostic tools. As revealed in Fig. 8, a nanosensor typically consists of three key components: sensing element, transducer, and signal processor.

### 5.1 Sensing element

This is the core part of the nanosensor that interacts with the target analyte (such as a chemical, biological, or physical entity).

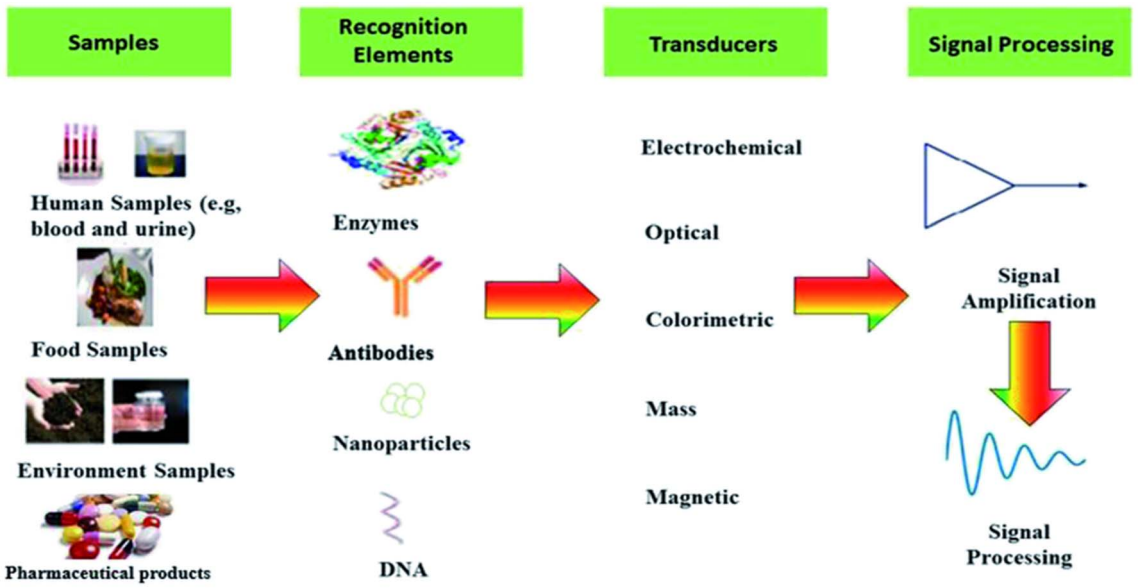


Fig. 9 This diagram depicts the sensing process. Sensors consist of two main components: a recognition element and a transduction element, reproduced from ref. 94, under Creative Commons Attribution 3.0 Unported Licence. The sensor captures input from the sample and transforms it into a signal. When the recognition element is composed of nanomaterials (with at least one dimension measuring between 1 and 100 nm), we refer to it as a nanosensor.

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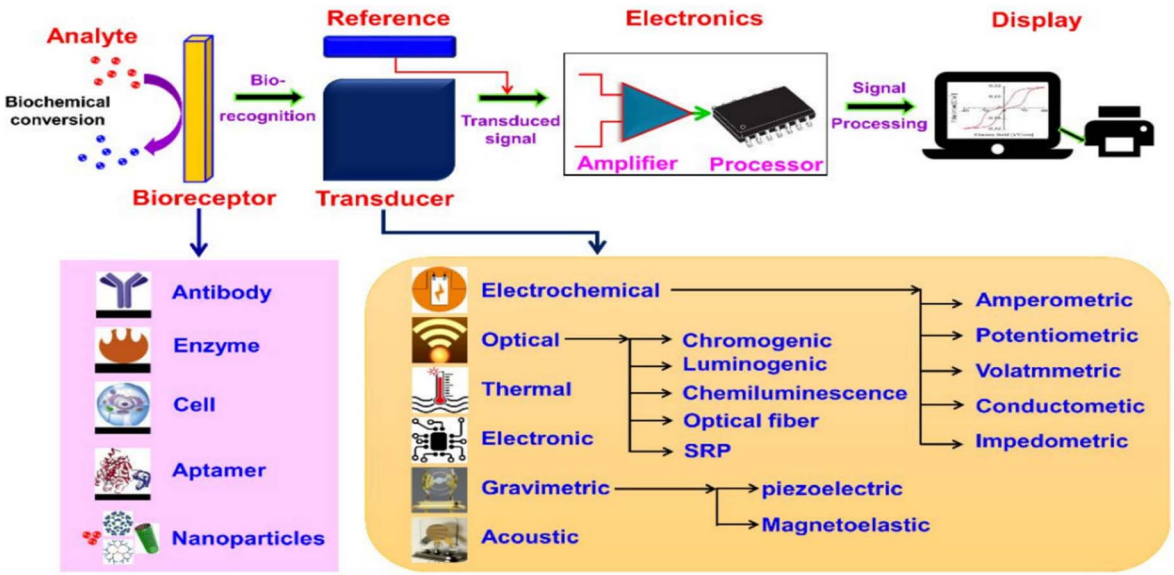


Fig. 10 Biosensors and their components, reprinted from ref. 92, copyright 2022, MDPI. Biosensors are composed of three key components: a bioreceptor, a transducer, and a signal processing unit. The bioreceptor, which could be an enzyme, antibody, nucleic acid, or cell, identifies the target analyte and triggers a biochemical reaction. The transducer then transforms this interaction into a measurable signal, which can be optical, electrochemical, piezoelectric, or thermal. At the same time, the signal processing unit amplifies and processes the output for analysis. Together, these elements allow biosensors to effectively and swiftly detect biological or chemical substances with high sensitivity and selectivity.

It is designed to be highly specific and sensitive to the property being measured (*e.g.*, a change in concentration, temperature, pH, or other environmental factors).

Highly sensitive nano-sensors offer unique strategies for signal detection and amplification, pushing detection limits to zeptomolar (zM) concentrations. Such sensing capabilities can be extremely useful in detecting biomarkers, diagnosing diseases early, and identifying recurrences after treatment (see Fig. 9). Examples of nano-sensor applications include the detection of DNA damage, cancer, viral infections, cardiovascular diseases, and Alzheimer's disease. Examples of sensing elements include nanoparticles, nanowires, or other nanomaterials with unique surface properties.

### 5.2 Transducer

The transducer is responsible for converting the interaction of the sensing element with the target analyte into a measurable signal. This could be an optical, electrical, mechanical, or thermal signal (see Fig. 10). Common transduction mechanisms include changes in fluorescence, electrical conductivity, or mechanical vibrations.

### 5.3 Signal processor

The signal processor amplifies, filters, and interprets the signal generated by the transducer. This converts the raw data into a readable output, allowing for the detection and analysis of the

Table 7 Transduction mechanisms of nano-sensors

| Nano-sensor | Transduction mechanisms | Area of applications | Ref. |
|---|---|---|---|
| Electrochemical nano-sensors | Changes in electrical properties (current, voltage, impedance) due to analyte interaction | Biomedical sensing, environmental monitoring | 93–97 |
| Optical nano-sensors | Changes in light absorption, fluorescence, or surface plasmon resonance (SPR) occur when an analyte binds to nanostructured surfaces | Biomedical diagnostics, food safety | 98–102 |
| Mechanical/nano-cantilever sensors | The binding of the analyte induces a change in mass or surface stress, causing deflection or frequency shift in a nano-scale cantilever | DNA hybridization detection, chemical sensing | 103 and 104 |
| Thermal nano-sensors | Interaction with the analyte changes thermal conductivity or heat generation, which can be measured | Chemical reactions, catalytic studies | 105 and 106 |
| Magnetic nano-sensors | Detect magnetic nanoparticles or changes in the magnetic field due to analyte interaction | Medical imaging, pathogen detection | 107–109 |

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target. The signal processor can include circuits or algorithms that analyze the data for patterns or changes that correlate with the presence of the analyte.

**5.3.1 Types of transduction mechanisms.** Different nano-sensors use different transduction principles depending on the nature of the interaction and the type of analyte. Table 7 presents the transduction mechanisms of nano-sensors, along with their corresponding applications.

## 6. Advancement in nanosensor materials and their influence on sensor performance

Recent advancements in the fabrication of nanosensors present promising solutions to enduring challenges related to sensitivity and selectivity. The use of 2D materials like graphene and transition metal dichalcogenides contributes to an extremely high surface area, adjustable electronic characteristics, and abundant active sites, which enhance the detection of rare analytes. Hybrid nano-composites, which combine different materials, such as metallic nanoparticles with polymers or carbon-based nanostructures, leverage synergistic effects to improve signal transduction and minimize nonspecific interactions, thereby enhancing selectivity. Moreover, the integration of AI in nanomanufacturing allows for meticulous control over nanoscale structures and surface modifi-cations, refining sensor performance through predictive modeling and automated feedback mechanisms. In a real sense, these innovations in fabrication can extend detection limits, customize molecular recognition, and create reproducible, high-performance nanosensors that are effective for complex real-world applications.

Recent advancements in materials have greatly enhanced the development of nanosensors (see Fig. 11). These advancements have improved the performance, sensitivity, and potential appli-cations of nanosensors across various fields. Nano-sensors are devices that leverage the unique properties of nanomaterials to detect and respond to environmental changes, chemicals, biolog-ical agents, and physical properties at the nanoscale. The progress in nanosensor technology is largely attributed to innovations in nanomaterials, which provide superior capabilities compared to conventional materials. Many studies tend to focus on the performance of nanosensors primarily based on the nano-materials used, such as graphene, quantum dots, or metal nano-particles. However, this perspective can be misleading. The true sensing performance often depends not just on the material itself but also on factors like the nanostructure, morphology, and the integration of various nanotechnologies. For example, sensors might utilize nanowires decorated with nanoparticles, core–shell nanostructures, or hybrid nanocomposites that incorporate different nanomaterials to improve selectivity, sensitivity, or stability. This section will mainly focus on the new developments in materials that enhance the nano-sensors' performance in biomedical systems, and will explore the advantages of various materials, including nanocomposite materials, graphene and graphene oxide, carbon nanotubes (CNTs), quantum dots (QDs), metal nanoparticles, nanostructured polymers, organic materials, and bio-inspired materials. As shown in Fig. 11, this aspect focuses on how these materials can enhance the selectivity and sensitivity of sensors, improve mechanical properties and electrical conduc-tivity, reduce response times, facilitate miniaturization and inte-gration, and provide versatility, multi-functionality, flexibility, and wearability. Fig. 11 illustrates different types of nano-sensors, categorized by (1) their detection targets, (2) the materials they are made of, and (3) the signals used for information transmission.

### 6.1 Nanosensor development through nanomaterial integration

Nanomaterials play a crucial role in the development of nano-sensors. They possess unique properties that enhance sensing

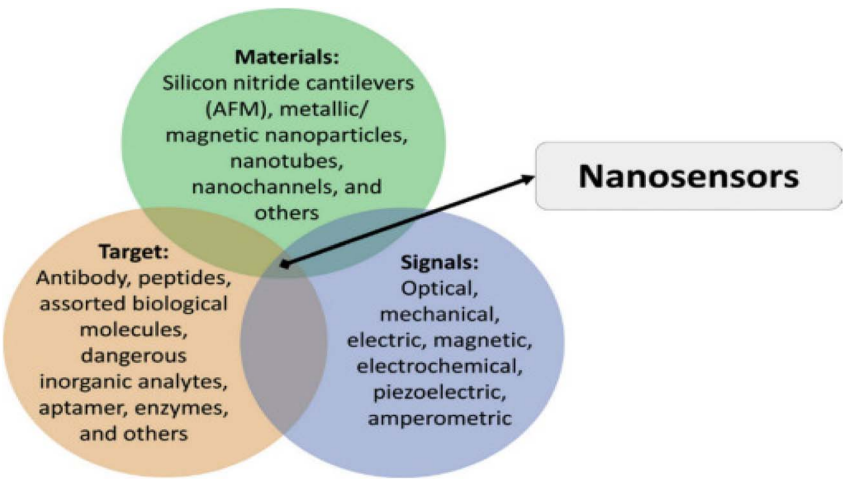


Fig. 11 Depicts the key components of nanosensors, reproduced from ref. 92, copyright 2022, with permission from MDPI. A typical nanosensor consists of three main parts: a recognition element, a transducer, and a signal processing unit. The recognition element interacts selectively with the target analyte at the nanoscale, often using nanomaterials like nanoparticles or nanotubes to boost sensitivity. The transducer then converts this interaction into a detectable signal, be it electrical, optical, magnetic, or mechanical. This signal is processed and amplified by the processing unit, allowing for accurate detection and quantification. Together, these components endow nanosensors with high sensitivity, quick response times, and miniaturization potential, making them valuable for diagnostics and environmental monitoring.

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Table 8 Various nanomaterials used in nanosensor development

| (1) Carbon-based nanomaterials | Descriptions | Applications | Ref. |
|---|---|---|---|
| Carbon nanotubes (CNTs) | It is known for its excellent electrical conductivity, high surface area, and chemical stability. CNTs are widely used in gas sensors, biosensors, and chemical sensors | CNT-based sensors can detect a wide range of chemical and biological substances, including environmental pollutants, pathogens, and even glucose for medical diagnostics. Their ability to functionalize with various chemical groups enhances their specificity and performance | 110–117 |
| Graphene | It provides a single layer of carbon atoms with exceptional electrical and mechanical properties. Its large surface area and high electron mobility make it suitable for detecting biomolecules and gases at ultra-low concentrations. Improving selectivity and sensitivity for specific analytes | Graphene-based nano-sensors are being used for detecting gases, biomolecules, and even pathogens. Graphene oxide (GO), a derivative of graphene, has additional functional groups that allow for easier modification | 118–120 |
| (2) Metal and metal oxide nanoparticles | Remarks | Applications | Ref. |
| Gold (Au), silver (Ag) nanoparticles | It is utilized in optical and electrochemical sensors due to its surface plasmon resonance (SPR) properties, enabling enhanced signal detection | Metal nanoparticle-based sensors are widely used in biosensors to detect biomolecules (like DNA, proteins, or pathogens) or environmental pollutants. Gold nanoparticles, for example, are often used in colorimetric sensors to detect heavy metals or gases | 121–123 |
| Zinc oxide (ZnO), titanium dioxide ($TiO_2$), iron oxide ($Fe_3O_4$) | Metal oxides are used for gas and humidity sensing owing to their semiconducting nature and reactivity with various analytes | Metal oxide nanomaterials such as ZnO, $TiO_2$, and $Fe_3O_4$ are widely used in nano-sensors due to their semiconducting nature, ease of synthesis, chemical stability, and high surface area. Each oxide offers distinct advantages that suit specific sensing applications | 124–126 |
| Quantum dots (QDs) | Semiconductor nanocrystals exhibit size-dependent fluorescence. Their tunable optical properties make them highly effective in optical and biosensing platforms | Quantum dots are utilized in optical nano-sensors to detect specific wavelengths of light or particular biomolecules. For instance, they are employed in biosensors for detecting DNA, proteins, and other biomarkers with high sensitivity and specificity | 127–129 |
| Polymeric nanomaterials. Examples include Polyaniline (PANI), Polypyrrole (PPy), Polythiophene (PT), Poly(3,4-ethylenedioxythiophene) (PEDOT) | Conductive polymers such as polyaniline (PANI) and polypyrrole (PPy) are used for chemical and biosensors due to their environmental stability, conductivity, and ease of functionalization | Polymeric nanomaterials provide a unique combination of electronic properties and chemical tunability, enabling the design of highly sensitive, selective, and flexible nano-sensors. Their integration into wearable, point-of-care, and environmental monitoring devices highlights their growing importance in next-generation sensing technologies | 130–134 |

Table 8 (*Contd.*)

| (2) Metal and metal oxide nanoparticles | Remarks | Applications | Ref. |
|---|---|---|---|
| 2D materials (beyond graphene) | Materials like molybdenum disulfide ($MoS_2$), black phosphorus, and hexagonal boron nitride are gaining attention for their layer-dependent properties and compatibility with flexible substrates | Transition metal dichalcogenides and black phosphorus are used in sensors for detecting gases, chemicals, and even biological species. They have also shown great potential in photodetectors and flexible electronics, expanding the possibilities for real-time and wearable sensing applications | 135 and 136 |

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mechanisms, including nanoparticles, nanowires, carbon nanotubes (CNTs), nanorods, and quantum dots (QDs)[79] (Table 8). The selection of nanomaterials relies on their sensing abilities, compatibility with the target analyte, stability, and fabrication ease. These materials are often combined with polymers, ceramics, or other substances alongside nanoparticles (like CNTs, graphene, or metal nanoparticles) to create composites that exhibit improved mechanical, electrical, or optical properties. These composites can be specifically designed for better sensor functionality, increasing sensitivity, stability, and selectivity. Their application areas include wearable sensors, environmental monitoring, and medical diagnostics. Nanomaterials can help address disease detection, treatment limitations, drug resistance, and targeted therapies in several ways.

Choi and Yoon[90] discussed various nanomaterials, such as nanoparticles, nanowires, and nanorods, that enhance the sensitivity and specificity of biosensors. This work highlights different detection strategies, including optical, electrochemical, and piezoelectric methods, that are employed in conjunction with nanomaterials to identify viral nucleic acids (see Fig. 12). The article underscores the significant potential of nanotechnology-assisted biosensors in improving the detection of viral nucleic acids, thereby contributing to better diagnostic tools and public health responses.

Wang *et al.*[91] summarized the application of nanotechnology in diagnosing and treating malignant tumors. Engineered nanoprobes and biosensors are reported to enable the detection of specific biomarkers, which facilitate early diagnosis and monitoring of tumor progression (as revealed in Fig. 13).

Ramesh *et al.*[92] examined various optical signal readout mechanisms employed in plasmonic biosensors, including colorimetric, Raman Spectroscopy, and fluorescence

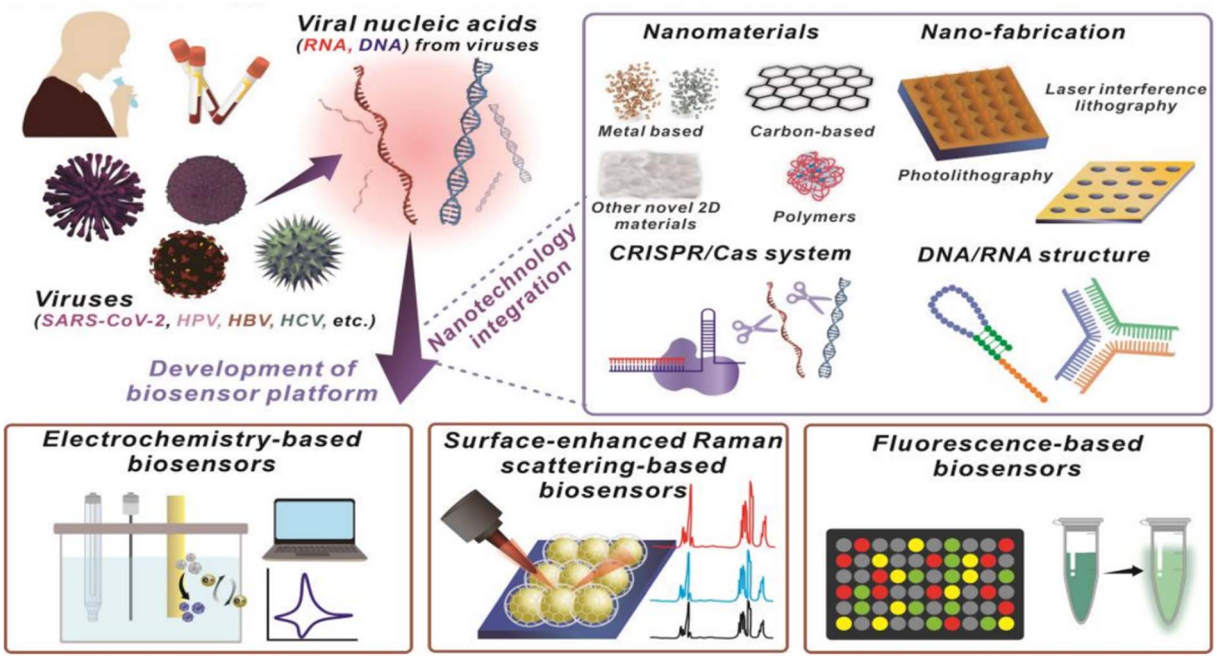


Fig. 12 Nanotechnology-assisted biosensors for the detection of viral nucleic acid, reproduced from ref. 80, copyright 2023, with permission from MDPI. By utilizing nanomaterials like gold nanoparticles, CNTs, graphene, and quantum dots, these biosensors improve sensitivity, specificity, and speed. The process involves a biorecognition element, such as DNA or RNA probes, fixed on a nanostructured surface to bind the target viral sequence. This interaction generates a measurable signal for quick and accurate viral detection, making these biosensors promising for early diagnosis and monitoring of infectious diseases.


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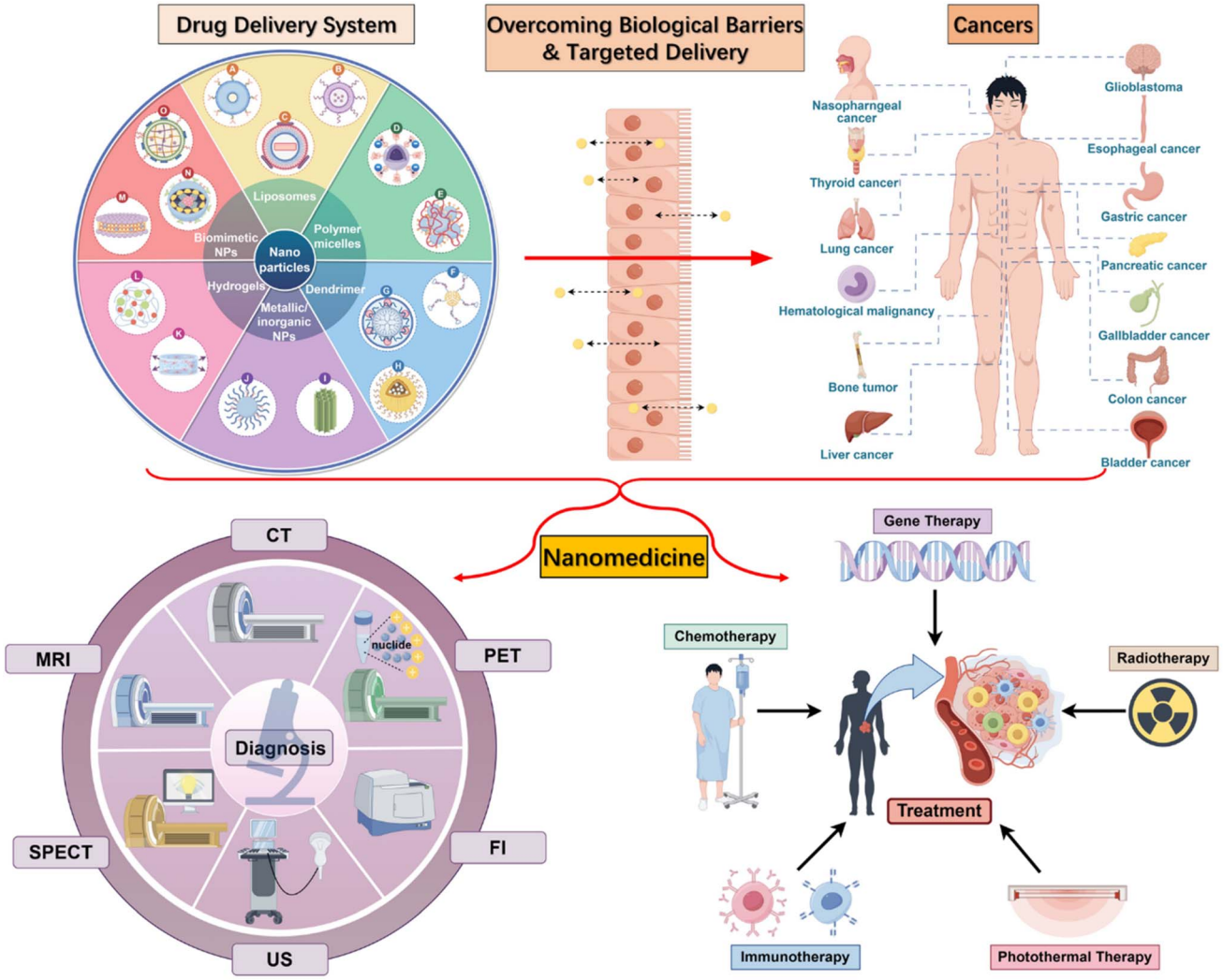


Fig. 13 Illustration of the applications of nanomedicine in cancer diagnosis and treatment, reproduced from ref. 91, copyright 2024, with permission from Springer Nature. Nanomedicine employs nanoscale materials and devices to enhance the precision, sensitivity, and effectiveness of cancer detection and therapy. In diagnostics, various imaging techniques, including CT (computed tomography), MRI (magnetic resonance imaging), PET (positron emission tomography), SPECT (single-photon emission computed tomography), ultrasound (US), and fluorescence imaging (FI), are improved through the use of nanoparticle-based contrast agents that enhance resolution and targeting specificity. In therapeutic applications, nanomedicine facilitates controlled drug delivery, targeted therapies, and combined theranostic approaches, which help minimize side effects and improve treatment outcomes.

techniques. These methods utilize the surface plasmon resonance (SPR) effect to enhance signal sensitivity, enabling label-free detection of biomarkers. Plasmonic nano-sensors represent a promising approach for the development of advanced diagnostic tools capable of rapid and accurate biomarker detection at the point of care. Continued advancements in nanomaterial design, sensor integration, and data analysis are expected to further enhance the applicability and effectiveness of these biosensors in clinical diagnostics.

Thwala *et al.*[137] examined the role of nanotechnology in enhancing point-of-care (POC) diagnostic devices, particularly for diseases prevalent in developing countries. The authors discuss recent advancements in nanomaterial-based diagnostics and their potential impact on healthcare in resource-limited settings. Future research in this area is focused on improving the stability, reproducibility, and affordability of nanomaterial-based diagnostic devices to facilitate their implementation in developing countries.[138]

Huang *et al.*[139] highlighted the significance of integrating nanotechnology with other emerging technologies, such as artificial intelligence and wearable devices, which could enhance the monitoring and treatment of infectious and inflammatory diseases.

Bardhan[138] provided an in-depth review of the role of nanomaterials in enhancing diagnostic, imaging, and therapeutic strategies for various diseases, with a particular focus on infectious diseases like COVID-19 and cancer. Continued research and development are essential to overcome existing challenges (such as potential toxicity concerns, the scalability of nanomaterial production, and regulatory hurdles) and fully realize the clinical benefits of nanomaterial-based approaches.

Tang *et al.*[140] examined design strategies for various nanosensors and the corresponding sensing nanomaterials,

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mechanisms, and properties. Structural modifications can impart nanomaterials with varied physical and chemical properties (such as electrical conductivity and luminescence) that interact with biomarkers, thereby altering the output signal. These nano-sensors enable continuous and real-time detection of fluctuations in cardiovascular disease biomarkers, offering direct evidence of their abnormal expression *in vivo* or *in vitro*.[141–143]

## 7. Understanding nanosensor behavior across chemical, biological, and physical domains

Due to the nanoscale of a nanosensor device, its behavior enables it to detect physical, chemical, or biological substances. Their heightened sensitivity arises from their small size and substantial surface area-to-volume ratio. Nano-sensors can be tailored to operate according to various mechanisms, including chemical, biological, and physical behaviors.

### 7.1 Chemical sensing mechanisms in nanosensors

It is a chemical sensor that is designed to detect specific chemical species, such as gases, ions, or biomolecules, by exhibiting measurable changes in properties like electrical conductivity, optical behavior, or mass upon exposure to the target analyte. For example, carbon nanotube-based sensors can detect nitrogen dioxide ($NO_2$) through changes in their electrical resistance, demonstrating the practical application of this sensing mechanism.[144] Tang *et al.*[145] discussed the use of CNT sensors for detecting various gases, including ammonia ($NH_3$). The sensors operate by exhibiting changes in resistance upon exposure to specific analytes, demonstrating the principle of chemiresistive sensing, as shown in Fig. 14.

This study also explained how the adsorption of analytes onto the CNT surface can affect conductance through several conditions, including the single-walled carbon nanotubes (SWCNT) electrode junction, charge transfer between the SWCNT and the analytes, and the connections between the tubes (as revealed in Fig. 9).[145,146]

Wang *et al.*[147] developed a gas sensor using multi-walled carbon nanotubes created through the microwave plasma-enhanced chemical vapor deposition method to detect gaseous $NH_3$. In this design, the nanotubes were placed underneath the electrodes, enabling the sensor to function at room temperature. The sensitivity exhibited a nearly linear relationship with gas concentration. The findings showed that the response time was approximately 180 seconds. However, due to $NH_3$'s strong attachment to the carbon nanotubes, it took more than 6 hours to return to the original state even in vacuum conditions.

Lee *et al.*[148] introduced a chemical sensor that shows exceptional performance in monitoring $NH_3$ levels. This sensor is

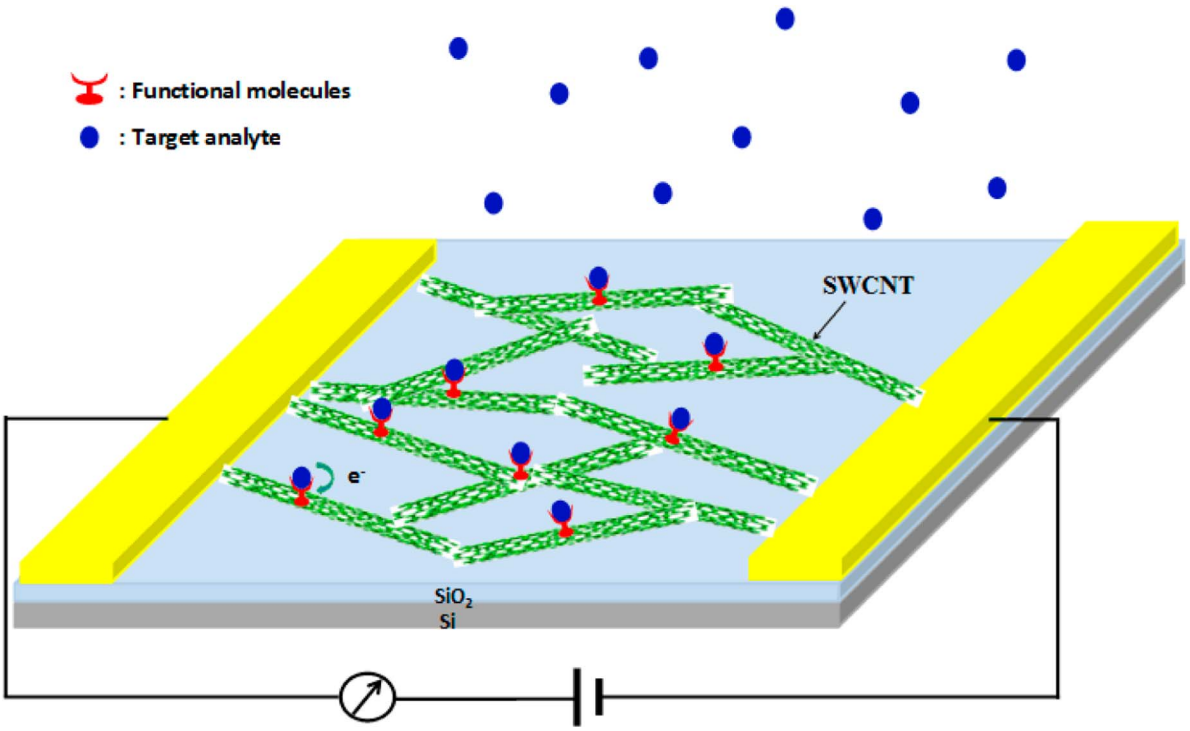


Fig. 14 Schematic diagram illustrating the typical configurations of a CNT chemiresistive sensor, reproduced from ref. 145, copyright 2017, with permission from MDPI. CNT-based chemiresistive sensors detect target gases or chemical species by measuring changes in electrical resistance that occur when analyte molecules interact with the surface of the CNTs. These configurations can involve either single-walled or multi-walled CNTs, arranged as individual tubes, thin films, or networked structures situated between metallic electrodes. When exposed to analytes, charge transfer or adsorption events at the CNT surface alter the carrier concentration, which in turn changes the resistance of the sensor. These configurations provide high sensitivity, rapid response times, and good reproducibility, making CNT chemiresistive sensors promising candidates for applications in environmental monitoring, healthcare diagnostics, and industrial processes.

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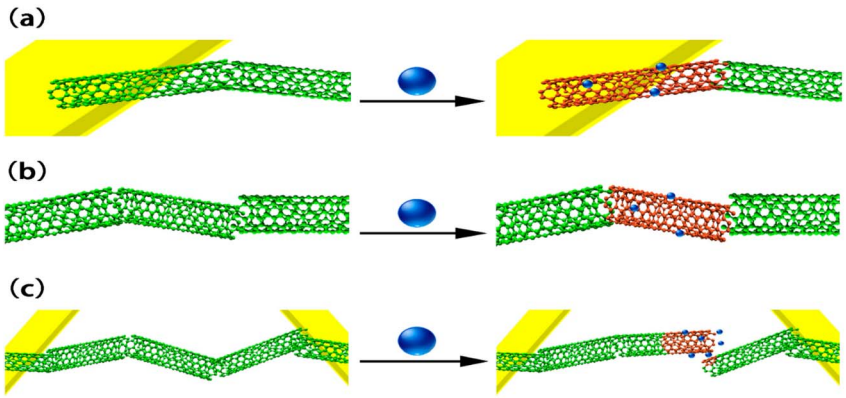


Fig. 15 Three ways that analytes influence the conductance of CNTs: (a) the SWNT-electrode junction: the presence of analytes can modify the contact resistance at the interface between SWNTs and the electrodes, which in turn affects the overall conductance of the sensor (b) charge transfer between the SWNT and analytes: when analyte molecules adsorb onto the surface of the SWNTs, they can either donate or withdraw electrons. This process alters the carrier concentration within the nanotubes, thereby impacting their conductance. (c) Inter-tube junction: in CNT sensors that are networked, interactions between analytes at the junctions of individual nanotubes can change the tunneling resistance. This change influences the overall electrical response of the sensor. These mechanisms work together to enhance the sensitivity and selectivity of CNT-based chemiresistive sensors, reproduced from ref. 145, copyright 2017, with permission from MDPI.

both transparent and flexible, constructed from functionalized SWCNTs integrated with Au nanoparticles (see Fig. 15). A notable increase in resistance was observed in the SWCNT film decorated with Au nanoparticles upon exposure to $NH_3$. The sensor demonstrates high sensitivity, with a limit of detection (LOD) estimated at approximately 255 parts per billion (ppb). It is believed that the electron donation from NH3 molecules absorbed on the Au nanoparticles enhances the electronic density, facilitating hole–electron recombination and leading to a decrease in hole current within the SWCNTs.

Avchukir *et al.*[130] created a novel impedimetric electrochemical sensor designed for the detection of the pesticide dichlorvos (DDVP). The detection mechanism relies on the inhibition of interfacial electron transfer; when DDVP interacts strongly with the modified electrode surface, it changes the interfacial properties of the electrode, resulting in measurable variations in impedance. These changes are then used to quantify DDVP levels. The combination of multi-walled carbon nanotubes (MWCNTs) and gold nanoparticles (AuNPs) on glassy carbon electrodes (GCE) enhances the sensing performance through a synergistic effect,

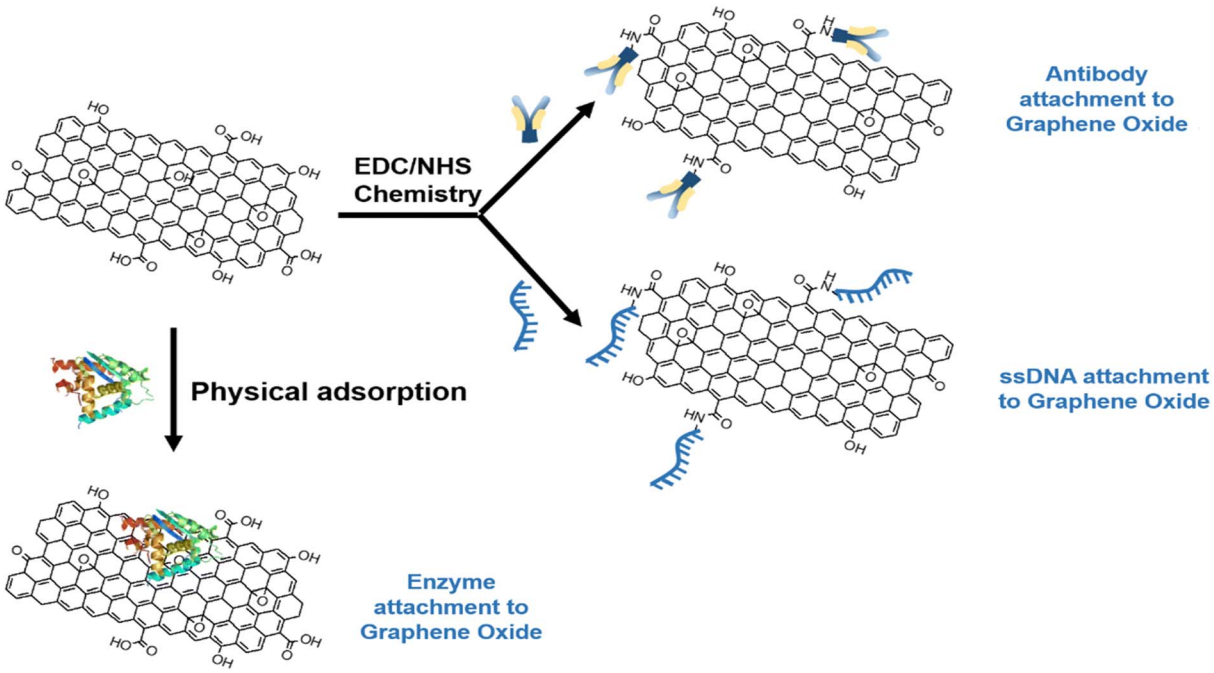


Fig. 16 Schematic showing the most common methods for attaching bioreceptors, such as antibodies, DNA, and enzymes, to graphene surfaces, reproduced from ref. 150, copyright 2018, with permission from Springer Nature. Table 9 summarizes published biosensor research, including information on sensor type, functionalization, target analyte, detection method, sensitivity, and key findings.

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Table 9 Overview of current advances in biosensor research

| Sensor type | Functionalization | Target analyte | Detection method | LOD/ sensitivity | Key findings | Ref. |
|---|---|---|---|---|---|---|
| Flexible chemical sensor | SWCNTs with Au nanoparticles | $NH_3$ (ammonia) | Resistance change | ~255 ppb | Transparent, flexible, high sensitivity *via* electron donation and hole recombination | 148 |
| Electrochemical biosensor | Antibodies | C-reactive protein (CRP) | Impedance spectroscopy | 0.1 ng $mL^{-1}$ | Label-free detection with excellent specificity and fast response | 151 |
| Fluorescent DNA biosensor | DNA aptamers | Thrombin | Fluorescence intensity change | 0.15 nM | High selectivity and real-time detection in blood plasma | 152 |
| Field-effect transistor (FET) | Graphene, antibody immobilized | COVID-19 spike protein | Current–voltage shift | 1 fg $mL^{-1}$ | Ultra-sensitive detection for point-of-care COVID-19 diagnostics | 153 |
| Optical biosensor | Enzyme-functionalized nanorods | Glucose | Colorimetric shift | 2 μM | Enzyme-catalyzed reactions change optical properties for rapid glucose monitoring | 154 |

which includes increased surface area, improved electron transfer kinetics, and better adsorption of the target molecule (DDVP). As a result, this method exhibits greater sensitivity and selectivity compared to bare electrodes or simpler modifications.

Jiang *et al.*[131] designed a flexible hydrogel sensor suitable for underwater applications. Traditional hydrogels used in wearable or underwater sensors tend to swell excessively in water, compromising their mechanical integrity and sensing

Table 10 Other physical stimuli detection

| Sensor | Materials | Applications | Advantages | Ref. |
|---|---|---|---|---|
| Temperature sensing | Nanomaterials like metal oxides, CNTs, and graphene are used for thermal sensing due to their temperature-dependent electrical conductivity | Thermoelectric, microheaters, and thermal imaging | The advantages of temperature sensors using nanomaterials like metal oxides, CNTs, and graphene include high sensitivity, fast response time, miniaturization, low power consumption, wide temperature range | 156–158 |
| Magnetic field detection | Magneto-resistive nano-sensors based on materials like $Fe_3O_4$, GMR (giant magnetoresistance) multilayers, or spintronic materials can detect extremely weak magnetic fields | Navigation systems, biomagnetic monitoring, and wearable magnetometers | Magneto-resistive nanosensors, constructed from materials such as $Fe_3O_4$, giant magnetoresistance (GMR) multilayers, and spintronic materials, offer several notable advantages. Their nanoscale architecture enables the detection of extremely weak magnetic fields with high sensitivity, making them suitable for applications in navigation systems, biomagnetic monitoring, and wearable magnetometers | 159 |
| Strain and force sensing | CNT and graphene-based composites are highly effective in strain sensors due to their high flexibility and mechanical strength | These sensors find their use in soft robotics, prosthetics, and athletic performance monitoring | CNT and graphene-based composites are highly effective in strain and force sensors due to their excellent flexibility and mechanical strength. These sensors are widely applied in soft robotics, prosthetic devices, and athletic performance monitoring.s | 160 and 161 |

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performance. The authors proposed a zwitterionic nanocomposite hydrogel, combining a zwitterionic polymer (poly[2-(methacryloyloxy)ethyl] dimethyl(3-sulfopropyl) ammonium hydroxide, *i.e.*, SBMA-based polymer) with bacterial cellulose nanofibers (BCNFs). This composition is meant to confer biocompatibility, self-adhesion, mechanical robustness, and crucially, anti-swelling behavior in aquatic (water) environments.

### 7.2 Biological sensing mechanisms in nanosensors

In this system, biosensors are often functionalized with biomolecules, such as antibodies or DNA, to enable the specific detection of target analytes, like antigens or proteins. These systems rely on molecular recognition to bind selectively to their targets with high specificity, translating this interaction into a measurable signal through mechanisms such as fluorescence or impedance changes. Park and Park[149] studied DNA Hybridization Sensors Based on Electrochemical Impedance Spectroscopy as a detection tool. In this work, electrochemical impedance spectroscopy (EIS) measures changes in the impedance of the biosensor surface upon analyte binding. This label-free technique detects alterations in the interfacial properties between the electrode and the electrolyte, providing real-time monitoring of biomolecular interactions. EIS-based biosensors are valued for their simplicity, cost-effectiveness, and suitability for point-of-care diagnostics.

Peña-Bahamonde *et al.*[150] discussed the latest advancements in graphene-based biosensor technology, particularly its applications in the life sciences. Their study employed various strategies for attaching biomolecules to the graphene surface, considering its chemical characteristics as presented in Fig. 16. Notable techniques include covalent bonding, which involves the use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and *N*-hydroxy succinimide for biomolecule coupling, as well as physisorption. These biosensors are especially important in life sciences and medicine, as their high sensitivity and specificity can greatly enhance patient care, allow for early disease diagnosis, and support effective pathogen detection (see Table 9).

### 7.3 Physical sensing mechanisms in nanosensors

This sensor can also be engineered to respond to physical stimuli such as temperature, pressure, force, or magnetic fields[155–160] (see Table 10). A common example is nanowire-based piezoresistive sensors, which exhibit changes in electrical resistance when subjected to mechanical pressure, enabling precise detection of physical changes at the nanoscale.[155]

## 8. Fundamental principles of nanosensor operation

The principle behind why a nanosensor works is rooted in nanoscale physical, chemical, or biological phenomena.[162–164] These principles enable the sensor to detect, interact with, or respond to a specific target (*e.g.* molecules, particles, or physical conditions) with high sensitivity and selectivity,[159–162] as described in Table 11. Some scientific principles that explain how and why nano-sensors work include Quantum Effects, Surface Area-to-Volume Ratio, Electrical Conductance Change, Optical Phenomena, Chemical Functionalization, Mechanical Deformation (Piezoelectric Effect), and Catalytic Reactions.[163–168]

- Quantum effects: at the nanoscale, quantum phenomena like quantum tunneling or quantum confinement become significant. These affect the electrical, optical, or magnetic properties of materials. In quantum dot-based sensors, electron energy levels change based on the environment, altering fluorescence. Quantum effects in nano-sensors arise from phenomena like quantum confinement, where electrons in nanomaterials exhibit discrete energy levels that change optical properties; quantum tunneling, which allows electrons to pass through barriers at the nanoscale, enabling highly sensitive detection; Coulomb blockade, which restricts electron flow to single-electron increments for ultra-precise sensing; and plasmonic resonance, where collective oscillations of surface electrons in nanoparticles shift in response to molecular interactions, allowing real-time, label-free detection, all of which make nano-sensors exceptionally sensitive and tunable for detecting minute changes at the atomic or molecular level.
- Surface area-to-volume ratio: nanomaterials have an extremely high surface-to-volume ratio, making them highly reactive and sensitive to changes. Nanomaterials exhibit an extremely high surface-to-volume ratio, meaning a large proportion of their atoms are exposed to the surface, which significantly enhances their reactivity and sensitivity, allowing nano-sensors to detect even minute changes in their environment, such as the presence of a single molecule or slight shifts in chemical composition.
- Electrical conductance change: many nanosensors rely on a change in electrical resistance or conductance when a target binds or interacts with the sensor surface. Electrical conductance change is a key principle in many nano-sensors, where the binding of a target molecule or exposure to a specific stimulus alters the flow of electrons through a nanomaterial such as carbon nanotubes, graphene, or nanowires, resulting in

Table 11 Principles behind nano-sensor operation

| Principle | How it enables sensing | Example material | Ref. |
|---|---|---|---|
| Quantum effects | Alters electron behavior to produce a measurable signal | Quantum dots | 162 |
| High surface area | More target interaction sites | Carbon nanotubes | 163 |
| Electrical conductance change | Signal changes upon target binding | Graphene, nanowires | 21 and 164 |
| Optical phenomena | Light absorption or emission shifts | Gold nanoparticles | 163 |
| Chemical functionalization | Specific target binding | DNA, enzymes, antibodies | 169 and 170 |
| Mechanical/Piezoelectric | Stress converts to an electrical signal | ZnO nanowires | 171 |
| Catalytic reactions | Generates measurable byproducts | Pt, Pd nanoparticles | 169 and 172 |

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Table 12 Nanosensor modeling for disease detection

| Disease | Sensor type | Nanomaterial | LOD | Modeling method | Ref. |
|---|---|---|---|---|---|
| Alzheimer's | Electrolyte-gated FET | Graphene | 447 ag $mL^{-1}$ | $\Delta I \propto [A\beta_{42}]$; calibration curve | 177 |
| Alzheimer's | Photonic crystal biosensor | Nanopillar + AuNP | 20 pg $mL^{-1}$ | Optical shift; $A\beta_{42}/A\beta_{40}$ ratio | 178 |
| Infectious (HBV) | FET aptasensor | Graphene + aptamer | 10 aM | $\Delta I = f([\text{target}])$; aptamer binding kinetics | 179 |
| Periodontitis | Colorimetric/LSPR | AuNP, ZnO nanofilms | 0.066 pg $mL^{-1}$ | Absorbance $\propto$ [biomarker]; enzyme rate | 180 |
| Various diseases/biomarkers (cancer, CVD, diabetes, neurodegenerative) | Fluorescence/quantum dots/CNT | Quantum dots, AuNP, CNT | Varies (fM–pM) | FRET/fluorescence *vs.* [analyte] | 181 |

a measurable change in conductivity that enables highly sensitive detection of gases, biomolecules, or environmental conditions.

• Optical phenomena: some sensors work based on changes in optical properties such as plasmon resonance or fluorescence. Optical phenomena play a crucial role in nano-sensors by leveraging changes in light absorption, emission, or scattering at the nanoscale, such as fluorescence shifts in quantum dots or surface plasmon resonance in metal nanoparticles, allowing for highly sensitive, real-time detection of molecular interactions, chemical changes, or biological events without the need for labels or complex processing.

• Chemical functionalization: nanomaterials can be functionalized with receptors (like enzymes, antibodies, DNA) that specifically bind to the target. The sensor transduces this binding into a measurable signal. Chemical functionalization involves modifying the surface of nanomaterials with specific chemical groups, biomolecules, or receptors, such as antibodies, enzymes, or DNA strands, to enable selective binding with target analytes, thereby enhancing the specificity and sensitivity of nanosensors by ensuring that only desired substances trigger a measurable signal.

• Mechanical deformation (piezoelectric effect): in some nano-sensors, mechanical stress from molecular binding or environmental change induces an electrical signal. Mechanical deformation in nano-sensors, often based on the piezoelectric effect, involves the generation of an electrical signal in response to mechanical stress or pressure applied to certain nanomaterials, such as zinc oxide or lead zirconate titanate nanowires, allowing the sensor to detect changes in force, vibration, or mass with high precision at the nanoscale.

• Catalytic reactions: catalysis at the nanoscale can generate detectable byproducts (*e.g.*, electrons, heat, or color changes). Catalytic reactions in nanosensors involve the use of nanomaterials, such as platinum, palladium, or metal oxides, as catalysts that accelerate specific chemical reactions; these reactions produce measurable signals (*e.g.*, changes in current, heat, or color), enabling the sensitive and selective detection of target substances like gases, glucose, or toxins in various environments.

### 8.1 Analytical model of a field-effect transistor-based nanosensor

A Field-Effect Transistor (FET)-based nanosensor detects target molecules (*e.g.*, DNA, proteins, toxins) by converting molecular interactions into electrical signals.[172,173] This sensor includes a semiconducting channel (such as carbon nanotubes, graphene, or $MoS_2$), source and drain electrodes for current flow, a gate (which can be back-gated, top-gated, or liquid-gated), and a biorecognition layer (like aptamers, antibodies, enzymes, *etc.*).[173] To describe the relationship between molecular binding and electrical response using mathematical models (see Table 12) based on semiconductor physics, electrostatics, surface chemistry, and kinetics,[174–176] as provided in eqn (1)–(5). For this sensor, sensitivity and repeatability are usually quantified in terms of changes in electrical, optical, or electrochemical signals relative to the analyte concentration, as given in eqn (6)–(8).

• Surface binding model (Langmuir isotherm)

Eqn (1) describes how much of the sensor surface is "covered" with analyte molecules, depending on concentration.

$$\theta = \frac{[A]}{K_D + [A]} \quad (1)$$

$\theta$: fraction of occupied binding sites (0 to 1), [A]: analyte concentration, $K_D$: dissociation constant.

• Charge density due to binding

The binding induces surface charge, which influences the gate voltage in the transistor as described in eqn (2)

$$Q_s = qN_s\theta \quad (2)$$

$Q_s$: total surface charge, $q$: elementary charge, $N_s$: surface density of binding sites.

• Threshold voltage shift

As more molecules bind, the surface charge increases, shifting the voltage required to turn on the FET

$$\Delta V_T = \frac{Q_s}{C_{ox}} \quad (3)$$

$\Delta V_T$: shift in threshold voltage due to surface charge, $C_{ox}$: gate oxide capacitance per unit area, $Q_s$: total surface charge.

• Drain current equation (Linear Regime)

With $V_T$ shifting due to binding, eqn (4) directly links biomolecular interaction to measurable current

$$I_{DS} = \mu C_{ox}\frac{W}{L}(V_{GS} - V_T)V_{DS} \quad (4)$$

$\mu$: carrier mobility, $W/L$: channel geometry (width/length), $V_{GS}$: gate-to-source voltage, $V_T$: threshold voltage, $V_{DS}$: drain-source voltage.

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Table 13 Limitations and challenges of metal/metal oxide decoration

| Limitation | Challenge | Explanation/Impact | Ref. |
|---|---|---|---|
| Nanoparticle aggregation | Metal or metal oxide nanoparticles tend to agglomerate | This reduces effective surface area and active sites, decreasing sensor sensitivity and reproducibility | 180–185 |
| Inhomogeneous distribution | Uneven dispersion on the nanomaterial surface | Leads to inconsistent performance across sensor batches and signal variability. Requires precise control in synthesis methods | 182–185 |
| High cost of noble metals | Au, Pt, and Pd are expensive and not sustainable for large-scale use | Increases the manufacturing cost of sensors, limiting their application in low-cost or disposable diagnostic devices | 181–185 |
| Stability under harsh conditions | Some metal oxides degrade or lose performance in humidity, temperature, or UV | For example, ZnO or $SnO_2$ can suffer from structural changes or surface poisoning in real-world environments | 181–185 |
| Complex fabrication methods | Synthesis techniques like ALD, hydrothermal, or electrodeposition need precise control | Requires specialized equipment and conditions (*e.g.*, temperature, pH, precursor concentration), making scale-up challenging | 181–185 |
| Weak interfacial bonding | Poor adhesion between the metal/oxide and the substrate nanomaterial | Leads to detachment, reduced stability, and poor signal transduction in devices, especially in wearable or flow-based sensors | 181–185 |
| Environmental sensitivity | Performance may be affected by oxygen, moisture, or contaminants | Metal oxides like $SnO_2$ or CuO are sensitive to ambient gases, leading to drift or false readings | 180–185 |
| Toxicity and biocompatibility concerns | Some metal oxides (*e.g.*, NiO, CuO) may be cytotoxic | Limits their use in biosensors or *in vivo* applications unless carefully encapsulated or coated | 181–185 |
| Poor long-term stability | Nanoparticles may oxidize, dissolve, or change morphology over time | This leads to loss of sensitivity, baseline drift, or sensor failure | 182–185 |
| Difficulty in regeneration | Decorated surfaces are often hard to clean or reuse | Limits the development of reusable or regenerative sensors, especially when used in biological environments | 184 and 185 |

• Time-dependent behavior (kinetics)

$$\theta(t) = \theta_{eq}\,(1 - e^{-k_{on}[A]t}) \quad (5)$$

$k_{on}$: on-rate constant, $t$: time.

• Sensitivity of a nanosensor

Sensitivity measures how the sensor's output changes with a change in the analyte concentration. It is generally defined as the slope of the calibration curve:

$$S = \frac{\Delta R}{\Delta C} \text{ or } S = \frac{\Delta I}{\Delta C} \quad (6)$$

where: $S$ = sensitivity of the nanosensor, $\Delta R$ = change in resistance (for resistive sensors), $\Delta I$ = change in current (for amperometric sensors), $\Delta C$ = change in analyte concentration.

Alternative for electrochemical sensors (like voltammetric or impedimetric nanosensors):

$$S = \frac{\Delta Z}{\Delta C} \quad (7)$$

where: $\Delta Z$ = change in impedance, $\Delta C$ = change in analyte concentration.

• Repeatability/reproducibility

Repeatability assesses how consistent the nanosensor response is under identical conditions. Lower relative standard deviation (RSD) indicates higher repeatability and reliability. A common metric is the RSD.

$$\text{RSD}(\%) = \frac{\sigma}{\bar{X}} \times 100 \quad (8)$$

where: $\sigma$ = standard deviation of the sensor response over multiple measurements, $\bar{X}$ = mean sensor response.

### 8.2 Surface functionalization

Surface functionalization plays a crucial role in producing nanosensors, especially when using nanomaterials like graphene, CNTs, metal nanoparticles, or quantum dots.[182,183] Functionalization enhances selectivity, sensitivity, stability, and biocompatibility by modifying the surface chemistry of the nanomaterial to interact specifically with the target analyte (*e.g.*, gases, biomolecules, toxins). Functionalization Strategies that are commonly used include covalent functionalization, non-covalent functionalization, bioconjugation, and metal and metal oxide decoration.[183,184]

• Covalent functionalization: this method involves introducing or reacting specific chemical groups (*e.g.*, –COOH, $–NH_2$, –OH) onto the surface of a nanomaterial, allowing further

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attachment of biomolecules, polymers, drugs, or sensor elements *via* robust covalent bonds. This chemical alters the surface reactivity, provides anchor sites for further functionalization, improves dispersibility in solvents or polymers, and enables targeted detection when used in sensors.

Challenges with covalent functionalization: this technique enables stable chemical bonding with nanomaterials, but it can disrupt their intrinsic properties, such as electrical conductivity or mechanical strength, by altering the material's original atomic structure. A pristine CNT has high electrical conductivity due to its intact $sp^2$ carbon network. If you covalently attach chemical groups (like –COOH or $–NH_2$), you may break some of those $sp^2$ bonds, converting them to $sp^3$ hybridized sites. This interrupts electron flow, leading to lower conductivity.

- Non-covalent functionalization: non-covalent functionalization refers to the modification of nanomaterial surfaces without forming covalent bonds. Instead, it uses weaker, reversible interactions, such as π–π stacking, van der Waals forces, electrostatic interactions, hydrogen bonding, and hydrophobic interactions. This approach preserves the intrinsic structure and properties (*e.g.*, electrical conductivity) of nanomaterials like CNTs, graphene, and other 2D materials. Unlike covalent functionalization, which can damage or disrupt the π-electron system in nanomaterials, non-covalent methods retain the electronic, optical, and mechanical integrity crucial for sensitive applications like field-effect transistor (FET) nanosensors or optical biosensors.

Challenges with non-covalent functionalization: less stable than covalent bonding.

- Bioconjugation: bioconjugation is a powerful technique in nanosensor fabrication that involves the chemical or physical linking of biomolecules (like antibodies, enzymes, DNA, or peptides) to nanomaterials (such as graphene, carbon nanotubes, gold nanoparticles, or quantum dots). This method enables nanosensors to selectively recognize and respond to biological targets, such as proteins, viruses, toxins, or small molecules. It actually involved the process of joining a biological molecule to another molecule or surface, typically a nanomaterial, using covalent, non-covalent, or bio-specific interactions. In nanosensors, this process is essential for target recognition, signal transduction, localization, and immobilization of biological receptors.

Challenges with bioconjugation methods: during conjugation, critical binding or active sites on enzymes, antibodies, or aptamers may be chemically modified or blocked, reducing their biological activity. Its impact reduces sensor sensitivity or false negatives. It is also time-consuming, costly, and harder to scale up for industrial applications.

### 8.3 Metal and metal oxide decoration

Metal and metal oxide decoration is a widely used technique in nanomaterial engineering and nanosensor fabrication, where nanoparticles of metals (like Au, Ag, Pt) or metal oxides (like ZnO, $TiO_2$, $SnO_2$, $Fe_3O_4$) are attached to the surface of other nanomaterials (*e.g.*, graphene, carbon nanotubes, polymers). This enhances various sensor properties, including sensitivity, selectivity, catalytic activity, electron transfer, and stability. This method utilizes the attachment or embedding of metallic or metal oxide nanoparticles onto the surface of a host nanomaterial to enhance its performance in applications such as gas sensing, biosensing, electrochemical sensing, catalysis, and energy devices (*e.g.*, supercapacitors, batteries). In addition, one of the technical issues affecting this method includes uneven dispersion on the nanomaterial surface. Yang *et al.*[185] conducted a study on the synthesis of $CeO_2$ (cerium dioxide) nanoparticles doped with different concentrations of Ni (nickel) at 1%, 2%, 3%, and 7% (molar ratio) using a coprecipitation method. This research led to the development of a resistive (chemi-resistive) sensor intended for the detection of volatile organic compounds (VOCs), specifically ethanol vapour. The sensor with 2% Ni-doped $CeO_2$ exhibited the best performance, achieving a response value of approximately 28 when exposed to 10 ppm ethanol. The response time for detecting ethanol was around 16 seconds, while the recovery time, returning to baseline after ethanol was removed, was notably rapid, taking about 1 second. Metal oxides degrade or lose performance in humidity, temperature, or UV, and other factors are described in Table 13. Table 13 highlight the limitations and challenges of metal/metal oxide decoration metal and metal oxide decoration.

## 9. Fabrication process of nanosensor structures

Nanosensors are instruments developed to identify and respond to stimuli on the nanometer scale.[186–189] Their characteristics, including sensitivity, selectivity, and response time, are significantly affected by their structure, which is defined by the fabrication techniques employed during their creation.

Designing a sensitive nano-sensor for a specific stimulus or analyte requires careful consideration of the appropriate nanomaterials, transduction mechanisms, and fabrication techniques to achieve the desired functionality. Gaining insights into how these fabrication methods influence nanosensors' structure is essential for enhancing their performance across various domains, including healthcare, environmental monitoring, and industrial applications. The selection of fabrication techniques depends on

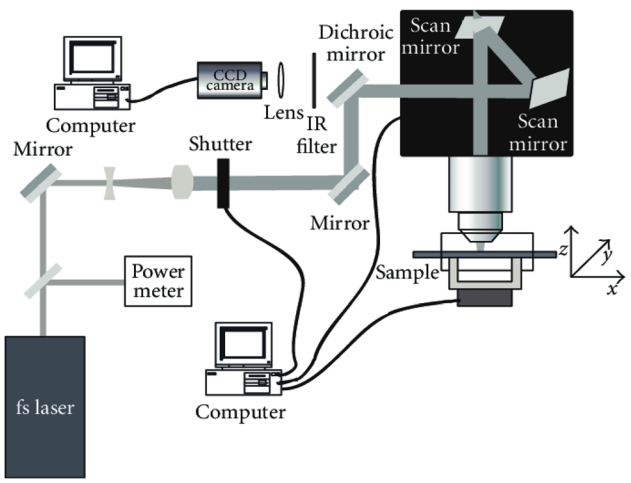


Fig. 17 Experimental setup for two-photon polymerization, reproduced from ref. 190, copyright 2008, Wiley.

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Table 14 Recent research on two-photon polymerization-applications, techniques, and key findings

| Year | Application | Technique/Focus | Main findings | Ref. |
|---|---|---|---|---|
| 2021 | Pre-cancer detection in pancreatic cysts | TPP-fabricated light scattering spectroscopic probe | Demonstrated an ultracompact fiber-based LSS probe fabricated *via* TPP for early detection of neoplasia in pancreatic cysts | 193 |
| 2024 | pH sensing | Optical microresonators made *via* TPP | Developed highly sensitive microresonators with reliable pH sensing capability using precise TPP structuring | 194 |
| 2020 | Mycotoxin detection | SERS on TPP nanostructures | Demonstrated that 3D nanostructures created *via* TPP significantly enhance Raman signals for detecting trace mycotoxins | 195 |
| 2023 | Microdevices | Integration of metal NPs with TPP | Outlined scalable strategies for incorporating functional nanoparticles into TPP for creating high-resolution, functional microdevices | 196 |
| 2025 | Integrated photonics | (3 + 1) D printing of core–clad waveguides | Successfully fabricated waveguides with independent core and cladding materials in 3D space using a single-step TPP process | 197 |
| 2025 | SERS substrate fabrication | Nanofabrication *via* TPP | Achieved reproducible and scalable fabrication of nanostructured surfaces optimized for strong SERS enhancement | 198 |
| 2023 | Quantum sensing | Complex 3D microscale TPP structures | Developed intricate 3D-printed geometries for quantum sensing platforms with optical and magnetic field sensitivity | 199 |
| 2025 | In-cell microfabrication | TPP inside living cells | Demonstrated for the first time that functional structures can be fabricated inside live cells using TPP without damaging cell viability | 200 |

the type of nanomaterials used, the sensing mechanism (electrical, optical, chemical, *etc.*), and the final application (*e.g.*, medical diagnostics, environmental monitoring).

There are several types of fabrication methods used in nanosensor fabrication, typically categorized into top-down, bottom-up, hybrid approaches, 3D printing, and coating techniques. Each method has its own advantages depending on the sensor type (*e.g.*, gas, chemical, biosensor), resolution requirements, and scalability. Among all the fabrication methods used to develop nanosensors, we will primarily focus on 3D printing techniques for creating a highly sensitive nanosensor.

### 9.1 Development of nanosensor structures *via* 3D printing methods

3D printing techniques have progressed to enable the creation of nano- and microscale features with high accuracy.[189] However, direct 3D printing at the nanometer scale remains very challenging, so many nanosensor parts are fabricated at the micro/nano level using hybrid methods. Aldhanhani *et al.*[186] confirmed that 3D printing of graphene composites is a rapidly growing interdisciplinary field with applications in energy storage, electronics, biomedical scaffolds, flexible devices, and EMI shielding. Aldhanhani *et al.*[187] demonstrated the feasibility of producing high-strength, graphene-reinforced parts using vat-photopolymerization 3D printing. This is valuable because VPP (DLP/SLA) is known for high resolution and surface finish, combining that with enhanced mechanical strength broadens its application. Ali *et al.*[188] explored using vat photopolymerization (VPP) 3D printing to manufacture light pipes/light funnels from a custom photosensitive resin. This study demonstrates that VPP 3D printing, often used for structural or decorative parts, can successfully produce functional optical components with complex geometries, broadening the scope of additive manufacturing. The main 3D printing techniques

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Table 15 Key challenges in TPP technology for nanosensor fabrication

| Challenge | Description | Ref. |
|---|---|---|
| Material limitations | Limited availability of photopolymers with desired mechanical, optical, or biocompatible properties<br>Difficulty in integrating functional materials like metals, semiconductors, or biomolecules | 193 and 195 |
| Process speed and scalability | TPP is inherently slow due to its voxel-by-voxel writing approach<br>Difficult to scale up for large-area or high-volume manufacturing | 196–199 |
| Structural resolution *vs.* throughput trade-off | High-resolution structures require slower writing speeds and finer optics<br>Optimization between resolution, fabrication time, and mechanical strength remains a challenge | 197 and 198 |
| Integration with functional materials | Difficulty in co-fabricating or embedding metal nanoparticles, quantum dots, or biosensing elements within polymer structures<br>Uniform dispersion and interface control are nontrivial | 136 and 144 |
| Biocompatibility and *in vivo* applications | Ensuring the use of non-toxic photoinitiators and biodegradable resins for *in vivo* applications remains an active area of research<br>Complex in-cell environments pose fabrication constraints | 193 and 200 |
| Optical setup complexity and cost | Requires expensive femtosecond lasers and high-NA objectives<br>Sensitive to alignment, optical aberrations, and laser stability | 194 and 197 |
| Post-processing and surface roughness | Need for post-curing, development, or smoothing steps<br>Surface quality can impact optical performance or cell adhesion in biomedical use | 198 |
| Real-time monitoring and feedback control | Lack of real-time feedback during fabrication limits precision in complex environments<br>Adaptive control systems are under development | 199 |
| Multi-material printing limitations | TPP is mostly single material; simultaneous multi-material fabrication is still limited | 196 |

suitable for making nanosensors or their parts include Two-Photon Polymerization (TPP)/Multiphoton Lithography, Inkjet Printing, Aerosol Jet Printing, Electrohydrodynamic (EHD) Jet Printing, and Fused Deposition Modeling (FDM) with nanocomposites.

**9.1.1 Two-photon polymerization (TPP)/multiphoton lithography.** Two-Photon Polymerization (TPP) is an advanced technique that enables the fabrication of complex, high-resolution 3D nanostructures, typically with sub-100 nm resolution[190–200] (see Fig. 17). TPP is a precise 3D micro-fabrication method used to create nano-sensors by directly writing intricate nanostructures into a photosensitive polymer with a tightly focused femtosecond laser. In this process, polymerization occurs only at the laser's focal point through the simultaneous absorption of two photons, allowing sub-diffraction resolution and true 3D control.

The fabricated structures, such as cantilevers, photonic crystals, microcavities, or fluidic scaffolds, serve as functional parts of the nano-sensor (see Tables 9 and 10). After fabrication, these structures are developed to remove unpolymerized material and are then functionalized with sensing elements, such as metal coatings (*e.g.*, gold for plasmonic sensing), quantum dots, biomolecules, or chemical receptors. The resulting nano-sensors can detect biological, chemical, or physical stimuli with high sensitivity and specificity, and they can be integrated onto optical fibers, microchips, or microfluidic platforms for various applications in biosensing, environmental monitoring, and nano-mechanics.[191,192] A few studies have used TPP technology to create sensing elements.

Sheil *et al.*[193] presented a novel ultracompact optical probe for light-scattering spectroscopy (LSS), fabricated using TPP, for detecting pre-cancerous changes in pancreatic cysts. This work demonstrates the power of TPP nanofabrication for creating highly precise, miniaturized biosensing tools that are clinically viable. It opens the door for non-invasive, early-stage cancer detection using advanced optical techniques in endoscopic procedures.

Saetchnikov *et al.*[194] illustrated how TPP enables high-resolution 3D nanofabrication in sensing devices. This work

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leverages TPP to create multiplexed arrays of "4D microcavities", tiny optical resonators whose geometry changes reversibly with pH. By fabricating hundreds of such cavities and coupling them optically, the system enables real-time pH detection with ultrahigh resolution (0.003 pH units). Tables 14 and 15 summarize recent advances and key challenges in TPP for biomedical, photonic, and sensing applications.

**9.1.2 Inkjet printing.** Inkjet printing is a digital, additive manufacturing technique that deposits functional "inks" containing nanomaterials (*e.g.*, nanoparticles, nanotubes, graphene, *etc.*) onto a substrate with high precision and no masks or etching[201] (Table 16). Inkjet printing is a precise, non-contact method used to create nanoscale sensor structures by depositing functional inks onto various substrates[202–209] (see Fig. 18). The process begins with formulating inks that have controlled viscosity (1–30 mPa s) and surface tension (25–50 mN $m^{-1}$), containing well-dispersed nanomaterials such as nanoparticles and graphene.

In drop-on-demand (DOD) inkjet printing, droplets are ejected as needed, using either thermal or piezoelectric mechanisms. The latter is preferred for biological inks, as it avoids heat. Once ejected, droplets travel through the air, spreading and adhering to the substrate, where their interaction is crucial and influenced by factors like surface energy and roughness. Common substrates include PET, PDMS, and textiles, ideal for wearable sensors. Post-processing may be necessary to enhance

Table 16 Inkjet-printed flexible sensors

| Authors & year | Main findings | Materials used | Applications | Ref. |
|---|---|---|---|---|
| Wang *et al.*, 2022 | Comprehensive review of inkjet-printed flexible sensors; emphasized process-material integration and performance tuning | Graphene, CNTs, AgNPs, conductive polymers | Wearables, IoT, healthcare monitoring | 202 |
| Kathirvelan, 2021 | Reviewed advances in printed wearable sensors; discussed power, flexibility, and ink-substrate compatibility | Carbon-based inks, silver nanoparticles | Wearable electronics, biosensors | 203 |
| Qi *et al.*, 2025 | Analyzed strain sensors *via* printing methods; linked conductivity, stretchability, and sensor response | CNTs, PEDOT:PSS, MXenes, elastomers | Soft robotics, human motion detection | 204 |
| Maddipatla *et al.*, 2020 | Reviewed techniques like inkjet, screen, and gravure for sensor printing; identified their pros and cons | Silver nanoparticle ink, carbon ink, ZnO | Medical sensors, disposable biosensors | 205 |
| Rincón-Iglesias *et al.*, 2025 | Demonstrated use of ferroelectric polymers in printed pressure/energy devices with enhanced piezoelectric response | PVDF-TrFE, PEDOT: PSS, AgNPs | Energy harvesting, tactile sensing | 206 |
| Baldini *et al.*, 2022 | Created a database (atlas) for printing large-area tactile sensors; optimized nozzle path and ink parameters | PEDOT: PSS, carbon ink, stretchable polymers | Robotic skin, haptics, e-textiles | 207 |
| Kong *et al.*, 2025 | Printed photodetectors using 2D materials; demonstrated optical performance on flexible substrates | $MoS_2$, graphene, $WS_2$, black phosphorus | Flexible photodetectors, optoelectronics | 208 |
| Mikkonen *et al.*, 2021 | Developed soft, capacitive pressure sensors using nanofibers and printed electrodes; achieved high sensitivity | Nanofiber mats (PU), AgNP ink | Tactile sensing, robotics, prosthetics | 209 |
| Torrisi *et al.*, 2012 | Demonstrated the first fully inkjet-printed graphene circuits; tunable conductivity and transparency achieved | Graphene inks (liquid exfoliated) | Transparent electronics, RF circuits | 210 |
| Malik *et al.*, 2024 | Reviewed paper-based inkjet sensors; highlighted affordability, versatility, and field deployment potential | Cellulose paper, silver ink, AuNPs, enzyme inks | Point-of-care testing, food safety, and environmental monitoring | 211 |

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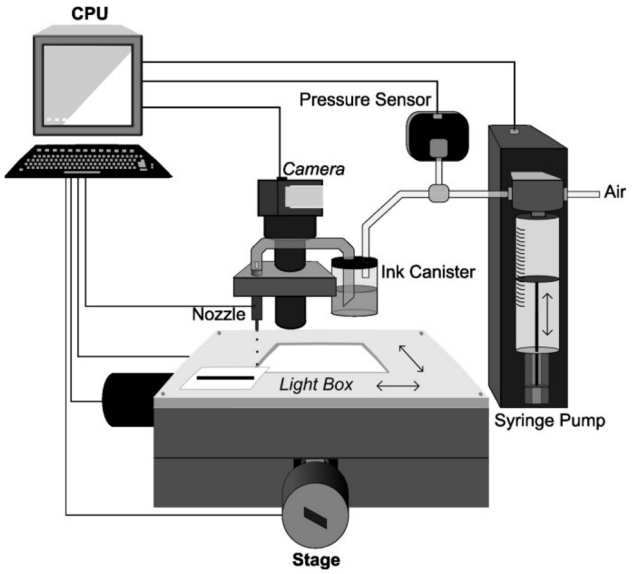


Fig. 18 The inkjet printing/imaging system consists of a nozzle, pressure sensor, ink canister, syringe pump, CPU, and stage. The imaging system includes a camera, light box, CPU, and stage, reproduced from ref. 201, copyright 2011, with permission from Springer Nature.

the properties of the inks, such as sintering for conductivity or UV curing for durability.[210–212] In summary, inkjet printing allows for controlled, scalable, and customizable fabrication of flexible and wearable nano-sensors. Table 17 presents key challenges in Inkjet Printing for nanosensor development.

**9.1.3 Aerosol jet printing.** Aerosol Jet Printing (AJP) is a powerful additive manufacturing technique that is especially well-suited for fabricating nanosensors due to its high-resolution, non-contact, and versatile material-deposition capabilities.[213–215] This technique is a direct-write, maskless printing technique that deposits fine droplets (1–5 μm in diameter) of functional inks onto substrates.[216,217] It allows precise control over the geometry, thickness, and placement of printed features. AJP works by atomizing functional ink into a fine aerosol mist, focusing it using a sheath gas into a tightly controlled stream, and then depositing it onto a substrate to create precise microscale or nanoscale patterns,[217–221] as shown in Fig. 19. Fapanni *et al.*[213] present a novel, additive, maskless AJP method to fabricate 3D-microstructured electrochemical sensors aimed at enhancing sensitivity by expanding electrode surface area. The printed microstructures, like parallel lines and grids, offer a significant boost in active area (up to 130%) without increasing the device's footprint. Kaindl *et al.*[215] explored the feasibility of AJP to deposit graphene and single-walled carbon nanotube (SWCNT) patterns onto realistically rugged substrates, specifically plasma-electrolytic-oxidized (PEO) aluminum blocks often used as heat sinks. This addresses a key challenge where most AJP applications focus on smooth and flat substrates.

**9.1.4 Electrohydrodynamic (EHD) jet printing.** Electrohydrodynamic (EHD) jet printing, also known as E-jet printing, utilizes an electric field to generate ultra-fine jets or droplets from a nozzle (see Fig. 20). This field-induced deformation forms a Taylor cone, and when the electric stress exceeds surface tension, tiny droplets or jets are emitted toward a grounded substrate.[222–224] This enables the deposition of features at submicron to nanometer resolution, far exceeding traditional inkjet limits. EHD jet printing is becoming an ultra-precise, versatile method for building nanoscale sensors for applications ranging from gas detection to wearable biosensors.[225–227] Its advantages include nanometric resolution, material diversity, compatibility with flexible and textured substrates, and the integration of smart manufacturing strategies (*e.g.*, ML control, multimodal patterning).

**9.1.5 Fused deposition modeling (FDM) with nanocomposites.** Fused deposition modeling (FDM) (or Fused Filament Fabrication) uses a thermoplastic filament melted and extruded to build parts layer by layer (see Fig. 21).[228–232] Nanocomposite variants incorporate nanofillers into the polymer feedstock to enhance functionality while still relying on the same fundamental extruder-nozzle-stage mechanics. Sheikh *et al.*[225] examined how CNTs, graphene, and cellulose nanofillers strengthen the performance of FDM-processed thermoplastics. It balances insights across materials, methods, applications, and modeling, and identifies clear directions for future research, particularly in scalable fabrication methods, filler dispersion, process standardization, and predictive modeling.[222] Guerra *et al.*[227] showed the potential of graphene nanoplatelets (GNPs)/polymer composites in advancing thermal management solutions, highlighting both the benefits and the processing challenges associated with FDM. This work exhibited that incorporating GNPs into polymer matrices significantly improves thermal conductivity. This enhancement is achieved by establishing a conductive network within the polymer, facilitating efficient heat dissipation.[230–233]

## 10. Summary, knowledge gaps, and future directions

The development of a nanosensor represents a complex interdisciplinary effort involving nanotechnology, materials science, chemistry, electronics, and engineering.[234–244] This review highlighted the essential design and fabrication processes guided by the FCBPSS model. In this work, the FCBPSS framework was used to define the essential requirements for nanosensor development by clarifying its function, adapting it to real-world contexts, ensuring reliable behavior, grounding it in scientific principles, and guiding the selection of suitable structures and stable operating states. To function effectively, the sensor must be tailored to detect low concentrations of biomarkers in diverse settings, delivering real-time quantitative measurements with high sensitivity and a low rate of false positives.[236–239,244–246] The sensor must perform reliably in challenging conditions, such as high humidity and temperature fluctuations, maintaining its functionality for extended periods without the need for recalibration, and being adaptable for use in portable devices or nanorobotics,[244] as presented in Table 18.

Moreover, the sensor must be effective in complex biological fluids like blood plasma or serum, adhering to biocompatibility

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Table 17 Key challenges in inkjet printing for fabricating nanosensors

| Category | Challenge | Description | Ref. |
|---|---|---|---|
| Ink formulation | Ink stability and clogging | Nanomaterials may agglomerate, settle, or clog nozzles due to poor dispersion or high particle size | 202, 203, 205, 210 and 212 |
| | Viscosity and surface tension limits | Only inks with specific viscosity (1–30 mPa s) and surface tension (25–50 mN $m^{-1}$) are printable; this limits material flexibility | |
| | Solvent compatibility | Solvents must be compatible with the substrate, printing system, and post-processing steps | |
| Printability and process control | Droplet consistency | Achieving uniform droplet size, volume, and placement is essential for reproducibility and resolution | 202, 203, 205, 210 and 212 |
| | Satellite droplets & misfires | Secondary droplets can reduce resolution and cause printing defects | |
| | Drying and spreading behavior | Ink may overspread or shrink unevenly on different substrates, leading to poor feature definition | |
| Resolution and feature size | Limited resolution (~20 μm) | While suitable for many applications, the resolution is lower than photolithography or electron-beam lithography | 202, 203, 205, 210 and 212 |
| | Trade-off between resolution and throughput | Higher resolution requires slower print speeds and finer nozzles, affecting scalability | |
| Material compatibility | Functional ink integration | Incorporating enzymes, biomolecules, or 2D materials without degrading them during printing or curing is challenging | 202, 203, 205, 210 and 212 |
| | Layer adhesion and intermixing | Multilayer printing may suffer from delamination or diffusion between layers | |
| Post-processing requirements | High-temperature sintering | Many conductive inks (*e.g.*, AgNPs) need thermal curing, incompatible with flexible substrates like PET or paper | 203, 210 and 212 |
| Scalability and standardization | Lack of industrial-scale uniformity | Inkjet-printed nanosensors are still largely lab-scale; scaling requires a consistent ink supply and reliable print heads | 202, 203, 205, 210 and 212 |
| | Cost of high-performance inks | Nanomaterial inks (*e.g.*, graphene, MXenes) are often expensive or not widely available | |

and safety standards suitable for point-of-care applications or lab-on-chip systems.[241–243] Desired performance characteristics of the sensor must include a rapid response time of under five minutes, high sensitivity to low biomarker levels, and strong selectivity to minimize cross-reactivity with non-target molecules.[255–264] Stability across multiple uses is essential, with less than 10% variation in results and minimal signal drift over time, even during refrigerated storage.[265–267] Operating on electrochemical detection principles, the nanosensor relies on redox reactions between the target biomarker and bi-ofunctionalized nanomaterials, utilizing biorecognition mechanisms like antigen–antibody binding or enzyme–substrate interactions. Ultimately, a high surface area structure with specifically immobilized antibodies or aptamers is crucial for

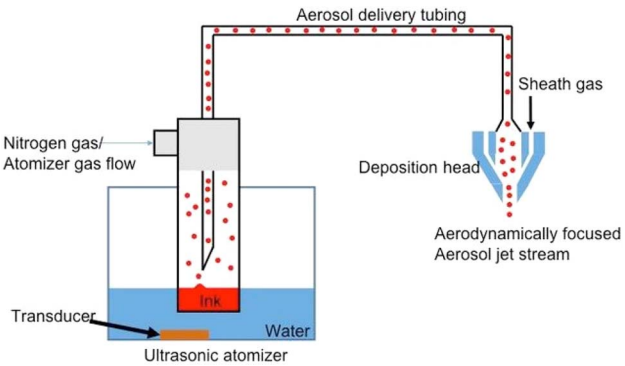


Fig. 19 Schematic of the aerosol jet printing process, reproduced from ref. 214, copyright 2017, IOP Publishing.

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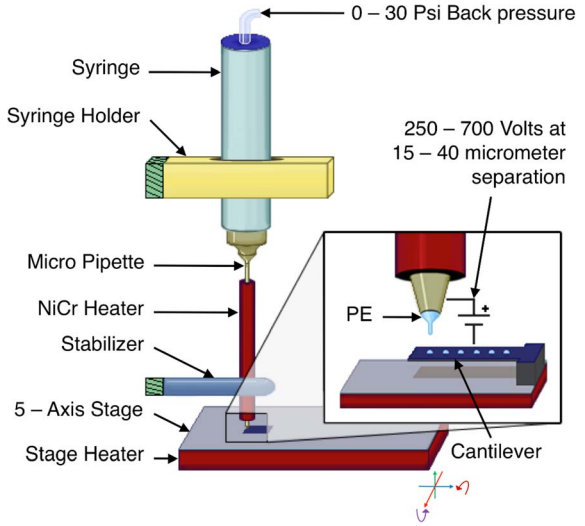


Fig. 20 Electrohydrodynamic (EHD) jet printing process, reproduced from ref. 223, copyright 2011, with permission from IEEE.

effective target binding. Meeting these comprehensive requirements is crucial to ensure the sensor's successful functionality. Our paper makes several key contributions to the field of nanosensor design by applying the FCBPSS framework to systematically identify design requirements, design issues that address current diagnostic challenges, and propose a structured approach for developing robust, high-performance nanosensors for biomedical applications. First, this paper highlights the critical design criteria for creating nanosensors intended for operation in physically demanding environments. This involves careful material selection, device architecture, packaging, and signal processing techniques to ensure stability, resilience, and sensitivity. Second, the paper emphasizes the need to enhance sensor selectivity for accurately identifying specific contaminants in complex environmental samples, as well as ensuring strong chemical stability to maintain sensor performance over time in harsh or reactive conditions. Third, this paper establishes the importance of using and developing multi-analyte detection strategies to monitor multiple pollutants simultaneously. Fourth, Research highlights the importance of developing anti-fouling coatings, such as PEGylation and zwitterionic surfaces. Furthermore, the addition of self-cleaning or responsive surfaces can greatly improve their long-term effectiveness. Fifth, research highlights the significance of utilizing advanced 3D printing and coating techniques aimed at enhancing the selectivity and sensitivity of sensors in complex biological environments. By exploring various methods, we recognize that each offers unique advantages tailored to specific sensor types such as gas sensors, chemical sensors, and biosensors.[247,250–252,254,268,269] When designed effectively, this sensor can exhibit improved sensitivity and responsiveness, allowing it to facilitate real-time health monitoring and disease management.[253,267,270] It can also support ultra-sensitive molecular diagnostics,[248,268] detect pathogens and bacteria,[249,254,269] and integrate into wearable and non-invasive biosensing platforms.[250,251] Additionally, it can be utilized in intelligent diagnostic systems for healthcare,[247,252] environmental monitoring, and point-of-care applications.[247–249] This work also considers critical factors like resolution requirements and scalability. Finally, it lays the groundwork for more effective and reliable sensors in biological applications, ultimately enhancing their performance in real-world scenarios.

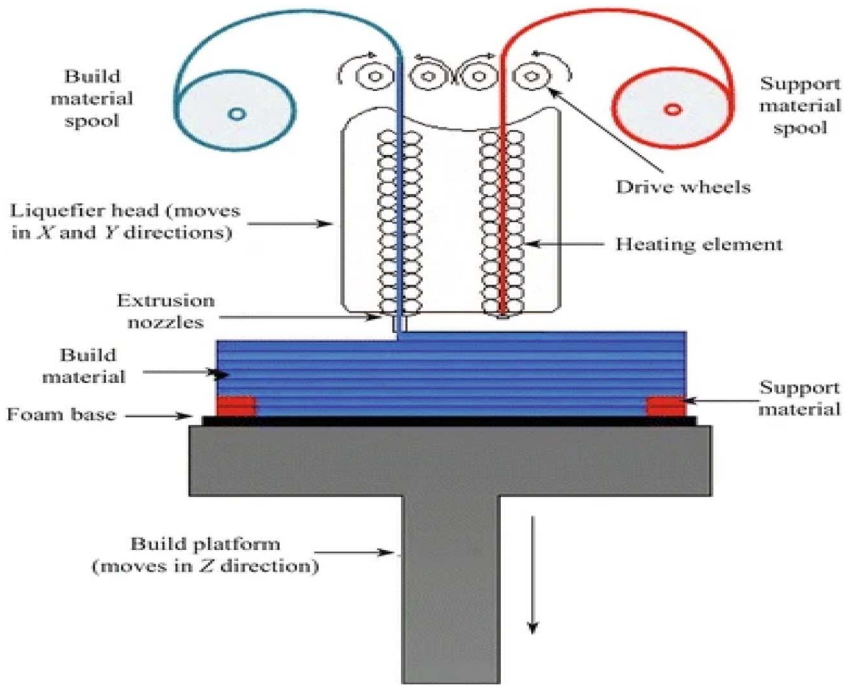


Fig. 21 A schematic diagram of a dual-head fused deposition modeling (FDM) 3D printer, reproduced from ref. 229, copyright 2015, with permission from Springer Nature.

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Table 18 Diagnostic scenarios and translational benefits enabled by nanosensors

| Application area | Translational outlook | Targets analyte | Ref. |
|---|---|---|---|
| Point-of-care (POC) diagnostics | Rapid, low-volume testing at bedside or community clinics enables immediate clinical decisions and reduces dependency on centralized labs | Infectious agents (SARS-CoV-2, influenza, HIV), cancer biomarkers (PSA, CEA), glucose, and creatinine | 240, 247, 248 and 249 |
| Wearable and continuous monitoring | Integration into flexible, skin-adherent, or implantable devices enables real-time tracking of physiological states | Glucose, lactate, electrolytes, stress hormones | 24, 250 and 251 |
| Digital health Ecosystems | IoT-enabled sensors feeding data to cloud platforms; supports remote diagnostics, telemedicine, predictive analytics | Cardiac biomarkers (troponin), neurodegenerative markers (amyloid-β, tau), and environmental toxins | 24, 252 and 253 |
| Early intervention and personalized medicine | Detect disease biomarkers before symptoms appear; allows proactive, personalized treatment and therapy adjustments | Cancer markers, metabolic disorder indicators, and infection markers | 250, 254 and 248 |
| Healthcare efficiency | Reduces hospital visits, lab testing burden, and treatment delays; facilitates population-level health monitoring | Multiple biomarkers, depending on the application | 24, 251, 252 and 249 |

### 10.1 Knowledge gaps in this field

This study assesses the effectiveness of the FCBPSS architecture in pinpointing crucial knowledge gaps (KGs) in this domain, which will contribute to the advancement of highly sensitive and selective nanosensors. To achieve meaningful progress in the development of nanosensors, it is essential to address various existing gaps.

KG-1: there is often a trade-off between selectivity (the ability to measure a specific analyte) and sensitivity (the ability to detect low concentrations). Improving both simultaneously is a significant challenge.

KG-2: the development of sensors capable of providing real-time monitoring in dynamic biological systems is still lacking. More innovation is necessary to create sensors that can adapt to changing conditions. Sensors can become unstable under varying environmental conditions (temperature, humidity, *etc.*), which impacts their reliability and lifespan. For example, the effects of biological substances (like proteins, cells, and metabolites) on sensor function and stability are not fully understood. Further studies are needed to evaluate how these factors influence sensor performance over time.

KG-3: analyzing and interpreting data from nanosensors is challenging. The complex data generated by these sensors requires advanced algorithms for effective interpretation. There is a necessity for enhanced data processing tools to facilitate real-time analysis and informed decision-making.

KG-4: there might be insufficient methods available to assess and validate whether the designs actually align with the stated requirements and needs. Gaps exist in the design of nanosensors that need to be addressed to ensure they meet system-level requirements and practical needs. Furthermore, there may be a lack of understanding of how to integrate user needs into the design process, leading to solutions that do not meet practical user requirements.

KG-5: identifying materials that maintain both high stability and sensitivity across diverse biological environments remains a significant challenge in the design of reliable biosensing platforms.

### 10.2 To close the knowledge gaps highlighted in Section 10.1

Nanosensors for diagnostics show great promise, enabling earlier, faster, more sensitive, personalized, and decentralized detection of disease. However, realizing this potential will require overcoming materials and manufacturing challenges, demonstrating real-world reliability and cost-effectiveness, integrating with data analytics and healthcare workflows, and achieving regulatory and commercial deployment. The future research directions to close the KG described in Section 10.1 are highlighted as follows;

To close KG-1: future research on enhancing the sensitivity and selectivity of nanosensors should prioritize the real-time detection of multiple analytes by improving both sensor sensitivity and selectivity.[271–274]

To close KG-2: efforts should focus on increasing sensor stability in challenging biological environments.[183,275] Understanding how sensors can be effectively integrated into living systems without causing adverse effects is essential.

To close KG-3: integrating nanosensors with artificial intelligence, machine learning, wearable devices, the Internet of Things, and cloud analytics for "smart diagnostics" and predictive health monitoring is crucial.[163,276,277]

To close KG-4: using frameworks like FCBPSS will help to ensure that designs satisfy system-level requirements and practical needs.[32–48] FCBPSS offers insights into how different parts of a system interact with each other, fostering a more comprehensive view of system integration. Categorizing requirements into functional, behavioral, and structural domains helps ensure that all aspects of user and system needs are considered and validated.

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To close KG-5: more research efforts are needed to identify and develop materials that can withstand harsh environments. First, use molecular simulations, surface analysis (*e.g.*, XPS, AFM), and *in situ* characterization (*e.g.*, QCM-D, impedance spectroscopy) to uncover how biological environments affect material interfaces. Second, employ machine learning to correlate material features and environmental parameters with performance metrics. Third, establish standardized testing protocols for comparing materials across studies. Fourth, identify trends between material properties (*e.g.*, surface chemistry, mechanical strength, hydrophilicity) and performance metrics (stability, sensitivity).[278–288]

## Ethical statement

This research does not involve human or animal participants.

## Consent for publication

The authors agree with the copyright transfer statement.

## Author contributions

B. O.: article writing, literature review, editing, and article draft preparation. A. O.: literature review, reviewing, and editing. M. A.: reviewing and editing and literature review. K. S.: editing and literature review. H. Y.: reviewing and editing. W. C.: reviewing and editing, and literature review. All the authors contributed to the manuscript and approved the final version.

## Conflicts of interest

The authors declare no conflicts of interest.

## Data availability

The authors confirm that the data supporting the findings of this study are available within the paper. Should any raw data files be needed in another format, they are available from the corresponding author upon reasonable request.

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