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DNA NANO BIOSENSORS - RECENT DEVELOPMENTS

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ABSTRACT

Biosensors are analytical devices combining biological recognition elements with physicochemical transducers to detect specific analytes. Since their inception, biosensors have evolved significantly, finding applications in medical diagnostics, pharmaceutical monitoring, food safety, and forensic science. DNA-based biosensors have emerged as transformative diagnostic tools due to their high sensitivity and specificity in detecting genetic mutations, pathogens, and disease biomarkers. These technologies rely on specific base-pair interactions for point-of-care applications while advancing personalized medicine. Nanotechnology has enhanced biosensor performance by addressing limitations like low sensitivity and poor signal transduction. Nanomaterials including nanoparticles, graphene, and quantum dots provide larger surface areas for biorecognition immobilization and amplify detection signals. This integration has enabled compact, portable biosensors with real-time monitoring capabilities and multiplexed assays for simultaneous analysis of multiple targets. The combination of DNA-based biosensors with nanotechnology has revolutionized diagnostics by offering faster results, simplified workflows, and improved detection limits. As research advances, these biosensors are expected to play a critical role in shaping the future of diagnostics across medical and industrial sectors.

Indexing Terms: Biosensors; DNA-based biosensors; Medical diagnostics; Nanotechnology; Point-of-care testing; Personalized medicine.

1. INTRODUCTION

Biosensors have emerged as revolutionary analytical devices that integrate biological recognition elements with physicochemical transducers to detect specific analytes. Since their inception in the early 20th century, biosensors have evolved significantly, finding applications in diverse fields such as medical diagnostics, environmental monitoring, food safety, and forensic science. The first biosensor, developed by Leland C. Clark Jr. in 1962 for glucose detection, marked the beginning of a multidisciplinary approach combining biology, chemistry, and engineering. Over the decades, advancements such as ion-sensitive field-effect transistors (ISFETs), fibre-optic sensors, and surface plasmon resonance (SPR) systems have enhanced biosensor performance, making them indispensable tools in modern science and technology [Bhalla, et al. **2016**; Vigneshvar, et al, **2016;** WP-01].

Among the various types of biosensors, DNA-based biosensors have gained particular importance in modern diagnostics due to their ability to detect specific DNA sequences with high sensitivity and specificity. These devices play a critical role in identifying genetic mutations, pathogens, and disease biomarkers, enabling early disease detection and personalized medicine. Compared to traditional diagnostic methods like PCR, DNA biosensors offer faster results and simpler workflows, making them suitable for point-of-care testing (POCT). Their integration with nanotechnology has further amplified their potential by improving detection limits and enabling multiplexed assays for simultaneous analysis of multiple targets [Vigneshvar, et al, **2016;** Mehrotra, **2016;** Ridhorkar, **2023**].

Nanotechnology has been a game-changer in the field of biosensors, addressing limitations such as low sensitivity and poor signal transduction. Nanomaterials like nanoparticles, graphene, and quantum dots provide a larger surface area for immobilizing bioreceptors and enhance signal amplification mechanisms. These innovations have enabled the development of compact, portable biosensors with real-time monitoring capabilities. Furthermore, nanotechnology has facilitated the creation of multiplexed sensors capable of detecting multiple analytes simultaneously, thereby increasing diagnostic efficiency across various fields. As a result, nano-enabled biosensors are now at the forefront of cutting-edge diagnostic technologies [Bhalla, et al, **2016**; Vigneshvar, et al, **2016;** Kulkarni, et al, **2022**].

This review explores the evolution of biosensors from their origins to modern advancements while focusing on the importance of DNA-based biosensors in diagnostics and the transformative role of nanotechnology in enhancing their performance [Mehrotra, **2016;** Patel, et al, **2016;** Vigneshvar, et al, **2016;** Huang, et al, **2023;** Ridhorkar, **2023**].

1.1 The Evolution of Biosensors

Biosensors are analytical devices that integrate a biological recognition element with a physicochemical transducer to detect specific analytes. They have become indispensable tools in various fields such as medical diagnostics, environmental monitoring, food safety, and forensic science due to their high sensitivity, specificity, and rapid response.

Historical Evolution of Biosensors

- *Early Beginnings* (**1906–1960s**)

The concept of biosensing began in 1906 when M. Cremer demonstrated the relationship between acid concentration and electric potential across a glass membrane. This laid the foundation for pH sensors [Bhalla, et al, **2016**; Ridhorkar, **2023**].

In 1956, Leland C. Clark Jr., known as the "father of biosensors," developed the first oxygen electrode (Clark electrode). He later introduced the concept of enzyme electrodes in 1962, which marked the creation of the first true biosensor for glucose detection as reported [Bhalla, et al, **2016**; Vigneshvar, et al, **2016**; Ridhorkar, **2023**].

- *Technological Advancement Era* (**1970s–1990s**):

Introduction of ion-sensitive field-effect transistors (ISFET) by P. Bergveld in 1970 [WP-01].

Development of the first commercial glucose biosensor by Yellow Springs Instruments in 1975. [Bhalla, et al, **2016**; WP-02]

Emergence of fibre-optic biosensors for gas detection and surface plasmon resonance (SPR)-based immunosensors in the late 1970s and early 1980s [Bhalla, et al, **2016**; WP-02].

By the 1990s, handheld devices like i-STAT blood analysers were introduced, making biosensors more portable and user-friendly [Bhalla, et al, **2016].**

- **Modern Era (2000s–Present)**

Integration of nanotechnology has revolutionized biosensor design, enabling miniaturization and enhanced sensitivity through nanomaterials like nanoparticles, graphene, and quantum dots [Vigneshvar, et al, **2016**; Ridhorkar, **2023**].

Advanced biosensors now include DNA-based sensors, aptamer-based systems, and wearable devices for real-time monitoring [WP-01; Mehrotra, **2016**].

Bio-FETs (Field-Effect Transistors) have been widely adopted for applications such as DNA hybridization and biomarker detection [WP-01].

The Key Components of Biosensors are primarily recognition element, transducer and signal processing unit in different suitable form.

- *Biological Recognition Element*s of the biosensors include enzymes, antibodies, nucleic acids, or cells that interact with the target analyte.
- *Transducer* converts the biological interaction into a measurable signal, using one of the electrochemical, optical, piezoelectric, or thermal methods.
- *Signal Processor* amplifies and processes the signal for display in a user-friendly format [WP-01; Mehrotra, **2016**].

The biosensors are very frequently used in many diverse fields including medical diagnostics, environmental monitoring, food safety and forensic investigations.

- Medical Diagnostics quite often involves glucose monitoring in diabetes management and biomarker detection for diseases like cancer besides several others.
- Environmental Monitoring deploys biosensors for detection of pollutants or toxins in water and air which may ultimately affect human health causing various diseases.
- Food Safety concerns are taken care of by monitoring food quality and detecting contaminants.
- Forensic Science identifies the genetic material in criminal investigations. [Bhalla, et al, **2016**; Vigneshvar, et al, **2016]**

The evolution of biosensors highlights a multidisciplinary approach combining biology, chemistry, physics, and engineering. From bulky laboratory instruments to portable point-of-care devices, biosensors have transformed how we detect and monitor chemical and biological substances with precision and efficiency [Bhalla, et al, **2016;** Mehrotra, **2016;** Vigneshvar, et al, **2016**; Katey, et al, **2023**; Ridhorkar, **2023**; WP-01; WP-02],

1.2 DNA-Based Biosensors in Modern Diagnostics

DNA-based biosensors, also known as genosensors, have emerged as transformative tools in modern diagnostics due to their ability to detect specific DNA sequences with high sensitivity and specificity. These biosensors are particularly valuable in identifying genetic mutations, pathogens, and biomarkers associated with various diseases. Below is an elaboration on their significant parameters to highlight their capabilities.

1. High Sensitivity and Specificity

DNA-based biosensors rely on the principle of complementary base-pairing, enabling them to detect even minute quantities of target DNA or RNA sequences. This makes them highly effective in early disease detection, such as identifying cancer biomarkers or viral genetic material (e.g., SARS-CoV-2). They can distinguish between closely related DNA sequences, such as single nucleotide polymorphisms (SNPs), allowing precise genetic analysis [Teles, and Fonseca, **2008;** Hua, et al, **2022**].

2. Rapid and Cost-Effective Diagnostics
Unlike traditional methods like PCR or ELISA, DNA biosensors provide faster results with simpler workflows. This procedure reduces the time and cost associated with laboratory-based diagnostics [WP-04; Mondal, et al, **2024**]. Recent advancements in nanotechnology have further lowered the production costs while enhancing the durability and performance of these biosensors [Hua, et al, **2022**].

3. Versatility in Applications
Disease Diagnosis based on DNA-based biosensors is used to detect genetic mutations linked to hereditary diseases, cancer biomarkers, and infectious pathogens [WP-03; Song, et al, **2006**]. This fundamental material based biosensing technology is currently being seriously explored for specialised areas like personalised medicine, and point of care testing in human healthcare management.

Personalized Medicines identify the patient-specific genetic markers to enable the biosensors in providing data for preparing tailored treatment plans.

Portable DNA biosensors allow for decentralized testing in clinics or remote areas leading to improved access to the healthcare services even in remote areas [Teles, and Fonseca, **2008;** WP-04].

4. Integration with Nanotechnology
The incorporation of nanomaterials like graphene, carbon nanotubes, and quantum dots has significantly enhanced the sensitivity and detection limits of DNA biosensors. These materials provide a larger surface area for immobilizing DNA probes and improve signal transduction mechanisms [Hua, et al, **2022**; Mondal, et al, **2024].**

Nanoengineered platforms also enable multiplexed detection of multiple targets simultaneously, increasing diagnostic efficiency [Teles, and Fonseca, **2008].**

5. Early Detection and Monitoring
Early diagnosis is critical for diseases like cancer, where treatment outcomes depend on timely intervention. DNA biosensors can detect low-concentration of biomarkers at early stages, enabling proactive disease management [WP-04; Sohrabi, et al, **2014**].

They are also effective in monitoring disease progression or response to a therapy by tracking changes in genetic markers over time.

6. Simplified Sample Handling
DNA biosensors often require minimal sample preparation compared to conventional techniques. They can work directly with complex biological samples like blood or saliva without extensive preprocessing [Song, et al, **2006;**Teles, and Fonseca, **2008**].

7. Potential for Real-Time Analysis
Advances in electrochemical and optical transduction methods allow real-time monitoring of hybridization events. This capability is crucial for applications like drug screening and environmental monitoring [WP-03; Mondal, et al, **2024**].

8. Challenges Addressed by DNA Biosensors
Traditional diagnostic tools often face limitations such as high costs, labour-intensive procedures, and the need for skilled personnels to carry out the test schedules. DNA-based biosensors address these challenges by offering user-friendly designs suitable for both clinical and non-clinical settings [WP-04; Song, et al, **2006**].

DNA-based biosensors have revolutionized the modern diagnostics by providing fast, accurate, and cost-effective solutions for detecting genetic material linked to diseases. Their integration with nanotechnology and potential for point-of-care applications make them indispensable tools in developing personalized medicine and global health initiatives. As research continues to refine their designs and functionality, these biosensors are expected to play an even greater role in shaping the future of diagnostics in human health care [Song, et al, **2006;**Teles, and Fonseca, **2008;** Sohrabi, et al, **2014;** Hua, et al, **2022;** Yu, et al, **2023;** Mondal, et al, **2024**; WP-03; WP-04].

1.3 Role of Nanotechnology in Enhancing Biosensor Performance

Nanotechnology has revolutionized the field of biosensors by significantly improving their sensitivity, specificity, portability, and cost-effectiveness. The integration of nanomaterials into biosensor designs has addressed many limitations of conventional biosensors, such as low detection limits and poor signal transduction. The role of nanotechnology in enhancing biosensor performance is described to highlight the recent development in this context.

1.3.1 *Enhanced Sensitivity and Lower Detection Limits*

a) High Surface Area to Volume Ratio features inherent in nanomaterials, such as nanoparticles, graphene, and carbon nanotubes, provide a large surface area for immobilizing bioreceptor molecules (e.g., DNA, enzymes, and antibodies). This increases the likelihood of target-analyte interactions, enabling the detection of extremely low concentrations of analytes [Holzinger, et al, **2014].**
b) Signal Amplification has been realised using nanomaterials that enhance the transduction process. For example: Gold nanoparticles improve optical

detection by enhancing plasmonic resonance. Quantum dots emit strong fluorescence signals for optical biosensors [Holzinger, et al, **2014].**

1.3.2 Improved Specificity
Nanomaterials enable precise functionalization with biological recognition elements (e.g., DNA probes or antibodies) through covalent or non-covalent binding strategies. This ensures selective binding to the specific target analytes while minimizing non-specific interactions [Holzinger, et al, **2014**].

Advanced nanostructures, such as nano plasmonic architectures, allow for highly specific detection mechanisms like surface plasmon resonance (SPR) and interferometry [WP-05].

1.3.3 Miniaturization and Portability
Nanotechnology has facilitated the development of compact, portable biosensors suitable for point-of-care testing (POCT). For instance, nano-plasmonic biosensors are smaller and simpler than traditional SPR systems while maintaining comparable sensitivity [WP-05]. Microfluidics integrated with nanomaterials allows for producing miniaturized lab-on-a-chip devices capable of performing multiple assays simultaneously [Lim, et al, **2015**].

1.3.4 Faster Response Times
Nanoscale materials reduce diffusion distances for analytes and enhance reaction kinetics, leading to faster detection times. This is particularly useful in real-time monitoring applications [Holzinger, et al, **2014**; Lim, et al, **2015**].

1.3.5 Multiplexing Capability
Nanotechnology enables multiplexed detection by incorporating multiple nanostructures or nanomaterial layers that can simultaneously detect various analytes in a single assay. This is crucial for applications requiring high-throughput analysis, such as disease biomarker screening [Wang, et al, **2020**].

1.3.6 Improved Signal Transduction
Nanomaterials serve as efficient transducers by converting biological interactions into measurable signals. For example, carbon nanotubes and graphene enhance electrochemical signal transduction due to their excellent conductivity. Plasmonic nanostructures improve optical signal generation by confining light waves at the nanoscale [WP-05; Holzinger, et al, **2014**].

1.3.7 Applications Across Fields
- **Medical Diagnostics**

Nanomaterial-based biosensors are used for detecting disease biomarkers (e.g., cancer markers, infectious pathogens) with high precision [Wang, et al, **2020].**

- **Environmental Monitoring**

Detection of pollutants and toxins is enhanced using nanostructured materials that improve sensitivity and portability [Lim, et al, **2015].**

- **Food Safety**

Rapid identification of contaminants is achieved through nano-enabled biosensors.

1.3.8 Challenges to Address
Nanotechnology has overcome several challenges faced by traditional biosensors:
- Improved selectivity through targeted functionalization.
- Enhanced reproducibility by controlling particle morphology and surface interactions during manufacturing [Wang, et al, **2020**].
- Automation and miniaturization for practical applications in resource-limited settings [Lim, et al, **2015**].

1.3.9 Future Directions
1. Further advancements in nanomanufacturing processes will improve reproducibility and robustness for clinical applications.
2. Development of cost-effective nano-enabled POCT devices will expand their use in low-resource settings.
3. Integration with artificial intelligence (AI) and Internet of Things (IoT) will lead to smarter biosensing platforms capable of real-time data analysis.

Nanotechnology has fundamentally transformed biosensor performance by addressing key limitations in sensitivity, specificity, and portability while enabling innovative applications across diverse fields. As research continues to advance, nano-enabled biosensors are expected to play an even greater role in diagnostics and monitoring systems worldwide [Holzinger, et al, **2014;** Lim, et al, **2015;** Wang, et al, **2020;** Ramesh, et al, **2023**; Desai, et al, **2024;** WP-05].

2. Fundamentals of DNA Nano Biosensors
DNA nano biosensors represent an outcome of cutting-edge technology that combines the specificity of DNA recognition with the enhanced capabilities offered by nanotechnology. These devices are designed to detect specific DNA sequences or biomarkers with high sensitivity and precision, leveraging principles such as hybridization, aptamers, and DNAzymes.

2.1 Basic Principles of DNA Biosensing
DNA hybridization is based on the complementary base pairing principle, where a single-stranded DNA probe binds to its target sequence. This interaction can trigger a measurable signal through various transduction methods. Hybridization-based sensors are widely used for detecting genetic mutations and identifying pathogens.

Aptamers are single-stranded DNA or RNA molecules that can bind to specific targets with high affinity, similar to antibodies. They are selected through a process called SELEX (Systematic Evolution of Ligands by EXponential Enrichment). Aptamer-based sensors offer advantages over traditional antibodies in terms of cost, stability, and ease of production.

A. *DNAzymes*

DNAzymes are catalytic DNA molecules that can perform chemical reactions, mimicking the function of enzymes. They are used in biosensors to amplify detection signals or catalyse reactions that produce measurable outputs.
DNAzymes are versatile tools in biosensor development due to their amenability to engineering them for specific functions.

B. *Integration of Nanotechnology with DNA Biosensors*

Nanomaterials like nanoparticles, graphene, and carbon nanotubes provide a large surface area for immobilizing DNA probes, enhancing the sensitivity and specificity of biosensors. These materials can also amplify detection signals through optical or electrochemical means.

C. Miniaturization and Portability

Nanotechnology enables the development of compact, portable biosensors suitable for point-of-care testing (POCT). This is crucial for decentralized healthcare applications. Miniaturized devices can easily perform multiple assays simultaneously, increasing diagnostic efficiency.

D. Advanced Detection Mechanisms

DNA origami structures and other nanoarchitectures allow for precise control over probe placement and signal transduction, leading to more sophisticated detection mechanisms. Examples include electrochemical genosensors that use 3D DNA structures for detecting microRNAs associated with diseases like lung cancer [Lien, **2025**].

E. Comparison with Conventional Biosensors

a. Sensitivity and Detection Limits

Nano DNA biosensors generally offer higher sensitivity and lower detection limits compared to conventional biosensors. This is due to the enhanced surface area and signal amplification provided by nanomaterials. For instance, nano-enabled biosensors can detect analytes at concentrations as low as picomolar or even femtomolar levels [Lien, **2025**; Ramesh, et al, **2022**].

b. *Portability and Multiplexing*

Conventional biosensors often require elaborate laboratory settings and are less portable. In contrast, nano DNA biosensors are designed to be compact and can perform multiplexed detection, making them more versatile for real-world applications.

The integration of nanotechnology allows for the simultaneous detection of multiple targets, which is challenging with traditional methods.

c. *Cost and Complexity*

While conventional biosensors may be simpler and less expensive to produce, nano DNA biosensors offer superior performance and flexibility, making them valuable for applications where precision and speed are critical.

However, the cost of nanomaterials and the complexity of their integration can be higher compared to those involved in the traditional methods.

The nano DNA biosensors leverage the strengths of both DNA recognition and nanotechnology to provide highly sensitive, portable, and versatile diagnostic tools. Their ability to detect specific DNA sequences with precision makes them invaluable in modern diagnostics and research applications as discussed in detail in several studies conducted by a number of research groups [Abu-Salah, et al, **2015;** Malhotra, and Ali, **2018;** Ramesh, et al, **2022**; Yuwen, et al, **2023;** Lien, **2025**].

1.3 Integration of Nanotechnology with DNA Biosensors

The integration of nanotechnology with DNA biosensors has transformed their design, functionality, and application, enabling unprecedented sensitivity, specificity, and versatility. By leveraging the unique properties of nanomaterials and DNA nanostructures, researchers have developed advanced biosensing platforms that address the limitations of traditional biosensors. Below is an elaboration on this integration:

1. *Role of Nanomaterials in DNA Biosensors*

Nanomaterials play a critical role in enhancing the performance of DNA biosensors by improving signal transduction, increasing surface area for probe immobilization, and enabling novel detection mechanisms. Key nanomaterials used include the followings.

a. Nanoparticles (e.g., gold and silver):

Gold nanoparticles (AuNPs) enhance optical signals through surface plasmon resonance (SPR) and improve electrochemical detection by facilitating electron transfer between the electrode and the analyte.
Silver nanoparticles are often used in fluorescence-based biosensors due to their high reflectivity.

b. Graphene and Carbon Nanotubes

These materials provide excellent electrical conductivity and a large surface area for immobilizing DNA probes. They enhance electrochemical signal transduction and enable label-free detection methods.

c. Quantum Dots

Quantum dots are used in optical biosensors for their strong fluorescence properties, allowing for highly sensitive detection of target DNA sequences.

d. DNA Origami Structures

DNA origami utilizes programmable base-pairing to create precise two- or three-dimensional nanostructures. These structures serve as scaffolds for assembling sensing elements with nanoscale precision, improving sensitivity and specificity [Raines, **2024**; Lien, **2025**].

2. *Significant Advantages of Nanotechnology Integration*

Enhanced Sensitivity

Nanomaterials amplify signals generated during molecular recognition events, enabling the detection of extremely low concentrations of target analytes (e.g., femtomolar levels) [Chao, et al, **2016**; Shen, et al, **2021**].

Improved Specificity

DNA nanostructures, such as tetrahedrons or cages, provide a controlled environment for probe-target interactions, reducing non-specific binding and false positives [Shen, et al, **2021**].

Miniaturization

Nanotechnology enables the development of compact and portable biosensors suitable for point-of-care testing (POCT). These devices can perform rapid diagnostics in clinical or resource-limited settings [Ramesh, et al, **2022**].

Multiplexing Capability

Nano-enabled platforms can integrate multiple probes on a single chip or structure, allowing simultaneous detection of multiple targets (e.g., different pathogens or genetic mutations) [Chao, et al, **2016;** Shen, et al, **2021**].

Real-Time Monitoring

Advances in nanotechnology facilitate real-time monitoring of dynamic biological processes through optical or electrochemical methods [Ramesh, et al, **2022**].

3. Applications in Precision Medicine

The combination of nanotechnology and DNA biosensors has significant implications for developing the precision medicine.

- Cancer Diagnostics:

Nano-enabled DNA biosensors can detect cancer biomarkers at early stages with high accuracy [Shen, et al, **2021].**

- Infectious Disease Detection:

CRISPR-based nano-biosensors, such as SHERLOCK and DETECTR, allow rapid and specific identification of viral or bacterial pathogens [Shen, et al, **2021**].

- Therapeutic Monitoring:

These biosensors are used to monitor genetic changes during treatment, enabling personalized therapeutic interventions [Chao, et al, **2016**].

4. Integration Challenges

Despite their advantages, integrating nanotechnology with DNA biosensors faces certain challenges:

1. Scalability

The production of nanomaterials with consistent quality at scale remains a challenge [Shen, et al, **2021**].

2. Stability

Some nanomaterials may degrade or lose functionality under physiological conditions, limiting their long-term use in clinical applications [Shen, et al, **2021**].

3. Regulatory Hurdles

The adoption of nano-enabled biosensors in healthcare requires rigorous validation to meet regulatory standards [Ramesh, et al, **2022**].

The integration of nanotechnology with DNA biosensors has revolutionized the field by enhancing sensitivity, specificity, portability, and multiplexing capabilities. From gold nanoparticles to DNA origami structures, nanomaterials have enabled the development of next-generation biosensing platforms tailored for applications such as cancer diagnostics, infectious disease detection, and therapeutic monitoring. While challenges remain in terms of scalability and regulatory approval, ongoing research continues to unlock new possibilities for nano-enabled DNA biosensors in precision medicine and global healthcare delivery systems [Xu, et al, **2009;** Chao, et al, **2016;** Shen, et al, **2021;** Ramesh, et al, **2022;** Raines, **2024**].

2.3 Comparison of DNA Biosensors with Conventional Biosensors

DNA biosensors have several advantages over conventional biosensors, which typically use enzymes, antibodies, or other biological molecules as recognition elements. Here's a comparison highlighting the key differences:

A. Advantages of DNA Biosensors Over Conventional Biosensors

a) Wider Detection Targets

DNA Biosensors can detect a broader range of targets, including nucleic acids, proteins, and small molecules, thanks to the versatility of DNA probes and aptamers [Hua, et al, **2022**].

The Conventional Biosensors are often limited to specific targets based on the antibody or enzyme used.

b) Durability and Stability

DNA Biosensors are more stable and resistant to degradation, offering a longer shelf life and better performance under harsh conditions [Hua, et al, **2022**].

In conventional biosensors the enzymes and antibodies can be sensitive to temperature and pH changes, affecting their stability.

c) Cost-Effectiveness

DNA Biosensors are generally less expensive to produce, especially with advancements in DNA synthesis technology [Hua, et al, **2022**].

Conventional Biosensors can be costly due to the complexity of antibody or enzyme production.

d) Customizability

DNA probes can be easily modified to change their affinity or specificity, allowing for tailored biosensing functions [Hua, et al, **2022**].

Conventional Biosensors deploying modified antibodies or enzymes can be more challenging and expensive.

e) Signal Amplification

DNA Biosensors deploy techniques like hybridization chain reaction (HCR) and catalytic hairpin assembly (CHA) can amplify signals, enhancing sensitivity [Hua, et al, **2022**].

Conventional Biosensors may not offer similar amplification strategies.

B. Challenges and Limitations

While DNA biosensors offer many advantages, they also face challenges such as:

Complexity in Design: Requires sophisticated design and engineering, especially for complex DNA structures.

Environmental Stability: Despite their stability, DNA biosensors can still be affected by environmental factors like nuclease activity.

Overall, DNA biosensors provide a promising alternative to conventional biosensors due to their robustness, customizability, and cost-effectiveness, making them suitable for a wide range of applications in biomedical analysis, food safety, and environmental monitoring [Vasdev, **2017**; Wu, et al, **2019;** Koopaee, et al, **2020;** Hua, et al, **2022;** Kalakonda, et al, **2023;** Mondal, et al, **2024**].

3. Functional DNA-Based Sensors

Functional DNA-based sensors utilize specific DNA structures to recognize and bind to target analytes, offering high sensitivity and specificity. Two prominent types of these sensors are **aptamer-** and **DNAzyme-based biosensors**.

Aptamer-Based Sensors

Aptamers are single-stranded DNA or RNA molecules that can bind to specific targets, including proteins, small molecules, and even cells. Aptamer-based sensors exploit this binding capability to detect a wide range of analytes.

Key Features

a. High Affinity and Specificity

Aptamers can be engineered to have high affinity for specific targets, allowing precise detection.

b. Stability and Durability

Aptamers are more stable than antibodies and can withstand harsh conditions, making them suitable for various applications.

c. Easy Modification

Aptamers can be easily modified to enhance their binding properties or to incorporate signalling elements.

Applications:

Clinical Diagnosis

Aptamer-based sensors are used for detecting biomarkers related to diseases such as cancer and infectious diseases.

Food Safety

They can identify pathogens and toxins in food samples via following mechanism:

Aptamers are immobilized on a sensor surface. Upon binding to the target, the aptamer's conformation changes, which can trigger a detectable signal through optical or electrochemical means.

DNAzyme-Based Sensors

DNAzymes are catalytic DNA sequences that can perform chemical reactions, similar to enzymes. DNAzyme-based sensors utilize these sequences to amplify detection signals with the following advantageous features.

a. Signal Amplification

DNAzymes can catalyse reactions that lead to significant signal amplification, enhancing detection sensitivity.

b. Versatility

DNAzymes can be designed to cleave specific substrates, releasing fluorescent or electroactive molecules that generate detectable signals.

c. Stability

Like aptamers, DNAzymes are stable and resistant to degradation.

Applications

- Used for detecting metal ions, nucleic acids, and other biomolecules in biomedical research.
- Can detect pollutants such as heavy metals in the context of Environmental Monitoring.
  The mechanism involves the following steps:
- DNAzymes are designed to cleave a substrate upon binding to a target.
- The cleavage releases a signalling molecule, which can be detected optically or electrochemically.

Both aptamer and DNAzyme-based sensors leverage the unique properties of DNA to achieve high sensitivity and specificity, making them valuable tools in various fields. [Abu-Salah, et al, **2015;** Li, et al, **2020;** Hua, et al, **2022;** Wang, et al, **2022;** Mondal, et al, **2024;**Wang, et al, **2024**].

Specific advantages of aptamers in biosensors
Aptamers offer several specific advantages when used in biosensors, making them a promising alternative to traditional antibody-based systems. Here are some of the key benefits:

Advantages of Aptamers in Biosensors
- High Specificity and Selectivity

Aptamers can bind to specific targets with high affinity and selectivity, reducing non-specific binding and false signals [Ning, et al, **2020**].
They can detect slight changes in target molecules, making them suitable for precise diagnostics [APS-02].

- Stability and Durability

Aptamers are more stable than antibodies, resisting degradation and maintaining activity under harsh conditions [Wandtke, et al, **2022;** Yang, et al, **2023].**
This stability allows for extended monitoring and regeneration of aptamer-based biosensors [APS-02].

- Ease of Synthesis and Modification:

Aptamers are easily synthesized and modified chemically, which facilitates their integration into various biosensing platforms [Yoo, et al, **2020;** Yang, et al, **2023].**

Their small size enables direct labelling with signalling molecules without affecting their binding properties [APS-02].

- **Low Immunogenicity**

Aptamers have low immunogenicity, making them suitable for in vivo applications without triggering immune responses [APS-01; Ning, et al, **2020**].

- **Cost-Effectiveness**

Production of aptamers is fast and inexpensive compared to antibodies, reducing costs for biosensor development [APS-02; Wandtke, et al, **2022**].

- **Real-Time and In-Field Detection**

Aptamers can be designed for real-time detection and are suitable for in-field applications due to their robustness and adaptability [Yoo, et al, **2020**].

- **Modularity and Multifunctionality**

Aptamer-based biosensors can be modularized to detect multiple targets simultaneously, enhancing their utility in complex diagnostic scenarios.

These advantages make aptamers highly versatile and effective components in biosensing technology, offering improved performance and practicality over traditional methods [APS-01; APS-02; Ning, et al, **2020;** Wandtke, et al, **2022;** Yang, et al, **2023;** Yoo, et al, **2020**].

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Advantages of Aptamers in Biosensors

1. **High Specificity and Selectivity**

Aptamers can bind to specific targets with high affinity and selectivity, reducing non-specific binding and false signals [APS -02; Ning, et al, **2020**].
They can detect slight changes in target molecules, making them suitable for precise diagnostics [ASP-01].

2. **Stability and Durability**

Aptamers are more stable than antibodies, resisting degradation and maintaining activity under harsh conditions [Wandtke, et al, **2022**].
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5. **Cost-Effectiveness**

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6. **Real-Time and In-Field Detection**

Aptamers can be designed for real-time detection and are suitable for in-field applications due to their robustness and adaptability [Yoo, et al, **2020**].

7. **Modularity and Multifunctionality**

Aptamer-based biosensors can be modularized to detect multiple targets simultaneously, enhancing their utility in complex diagnostic scenarios [Yoo, et al, **2020**; Gan, et al, **2022**].

These advantages make aptamers highly versatile and effective components in biosensing technology, offering improved performance and practicality over traditional methods [APS-01; APS-02; Ning, et al, **2020;** Yoo, et al, **2020;** Gan, et al, **2022**; Wandtke, et al, **2022**; Yang, et al, **2023**].

Recognition Elements in Biosensors - Aptamers and Antibodies
Here's a comparison of these two molecules in terms of specificity and sensitivity.

Specificity

Aptamers are known for their high specificity, often comparable to or even surpassing that of antibodies. They can be engineered to bind specifically to targets, including small molecules, proteins, and even chiral compounds, by forming precise three-dimensional structures that match the target's shape. The SELEX process ensures that aptamers are selected for their ability to discriminate between closely related targets, minimizing non-specific binding [Domsicova, et al, **2024**].

Antibodies also exhibit high specificity, generated through an immune response that tailors them to specific antigens. However, their specificity can be influenced by the complexity of the immune system's response, which may not always yield the desired level of specificity [APS-03].

Sensitivity

Aptamers can achieve detection limits in the range of micro-molarity to pico-molarity, which is comparable to or even better than the affinity of monoclonal antibodies [Domsicova, et al, **2024**]. Their small size and ability to penetrate tissues deeply enhance their sensitivity in detecting targets within complex matrices [Jeong, and Rhee Paeng, **2012**].

Antibodies are renowned for their high sensitivity, particularly in applications like ELISA assays. However, their sensitivity can be affected by factors such as stability and the need for specific conditions to maintain their activity [Jeong, and Rhee Paeng, **2012].**

Overall, aptamers offer advantages in terms of production ease, stability, and cost-effectiveness, while both aptamers and antibodies provide high specificity and sensitivity, making them valuable tools in biosensing applications as listed in Table 1 [APS-03; Jeong, and Rhee Paeng, **2012;** Ali, et al, **2019;** Bauer, et al, **2019;** Aljohani, et al, **2022;** Domsicova, et al, **2024**].

Table 1: Comparison Summary.

Feature	**Aptamers**	**Antibodies**
Specificity	High specificity through SELEX process, capable of distinguishing between closely related targets [APS-03; Domsicova, et al, **2024**].	High specificity generated through immune response, but can be variable [APS-03]
Sensitivity	Comparable or superior to antibodies, with detection limits from micro-molarity to pico-molarity [Domsicova, et al, **2024**].	High sensitivity, but can be affected by stability and conditions [Jeong, and Rhee Paeng, **2012**]
Production	In vitro synthesis, rapid production, and low cost. [Jeong, and Rhee Paeng, **2012;** Domsicova, et al, **2024**].	Requires in vivo immune response, longer production time, and higher cost [APS-03].

How do aptamers's maller size benefit their use in diagnostics?

The smaller size of aptamers compared to antibodies offers several benefits in diagnostic applications. The associated properties affected are such as improved tissue penetration, capability to target even smaller molecules, increased concentrations in smaller volumes rapid clearance the renal route, and ease of modification and conjugation.

Accordingly, the benefits of Aptamers' smaller size in diagnostics are summarised below.

- **Improved Tissue Penetration**

Aptamers can penetrate tissues more effectively due to their smaller size (typically 12-30 kDa), which is crucial for detecting targets within tissues or cells, especially in cancer diagnostics [APS-02, Thiviyanathan, and Gorenstein, **2012**]. This increased penetration allows aptamers to bind to targets that might be inaccessible to larger antibodies, improving diagnostic accuracy.

- **Targeting Small Molecules**

Aptamers can bind to small molecules (≥ 60 Daltons), which is advantageous for detecting low molecular weight targets that antibodies may not effectively recognize [APS-02]. Specificity for Small Targets: Their ability to specifically bind to small molecules enhances their utility in detecting a wide range of analytes, from ions to complex proteins.

- **Higher Concentration in Solutions**

Due to their lower molecular weight, aptamers can be present in higher numbers than antibodies in solutions of the same concentration, potentially increasing the sensitivity of diagnostic assays [APS-02]. This higher concentration can lead to stronger signals in diagnostic tests, improving detection limits.

- **Rapid Renal Clearance**

While rapid renal clearance can be a limitation for therapeutic applications, in some diagnostic scenarios, the small size of aptamers allows for quick distribution and localization to target sites, which can be beneficial for real-time diagnostics [Bruno, **2022**].

- **Ease of Modification and Conjugation**

Aptamers' small size facilitates chemical modifications that enhance their stability and functionality, making them suitable for integration with nanoparticles or other diagnostic platforms [Kaur, et al, **2018**]. Aptamers can be easily conjugated with nanoparticles, which protects them from degradation and enhances their diagnostic capabilities [Kumar Kulabhusan, et al, **2020**].

Overall, the smaller size of aptamers provides significant advantages in diagnostics by improving tissue penetration, enhancing target accessibility, and allowing for higher concentrations in solutions, which can lead to more sensitive and specific diagnostic tests [ASP-02; Thiviyanathan and Gorenstein, **2012;** Zhu, et al, **2015;** Kaur, et al, **2018;** Kumar Kulabhusan, et al, **2020;** Agnello, et al, **2021;** Bruno, **2022**].

Specific Examples of DNA Biosensors in Clinical Applications

i. Detection of SARS-CoV-2:
DNA-based biosensors have been successfully used for the rapid detection of SARS-CoV-2 during the COVID-19 pandemic. These biosensors employed CRISPR-Cas systems or electrochemical platforms to identify viral RNA with high sensitivity and specificity, enabling point-of-care testing in clinical settings.

ii. Cancer Biomarker Detection
DNA biosensors have been developed to detect cancer biomarkers like circulating tumor DNA (ctDNA) and microRNAs. For instance, biosensors utilizing gold nanoparticles and graphene oxide have demonstrated high accuracy in identifying mutations associated with breast and lung cancers.

iii. Antibiotic Resistance Genes
Clinical applications include the detection of antibiotic resistance genes in pathogens. DNA biosensors based on hybridization techniques have been employed to monitor resistance markers such as *bla* genes in bacterial infections, aiding in targeted antibiotic therapy.

iv. Genetic Disorder Screening
Portable DNA biosensors have been applied for prenatal screening of genetic disorders like Down syndrome by detecting specific chromosomal abnormalities in fetal DNA extracted from maternal blood.

v. Cardiovascular Disease Monitoring
Biosensors targeting specific DNA sequences linked to cardiovascular diseases, such as single nucleotide polymorphisms (SNPs) associated with hypertension or atherosclerosis, have been introduced for early diagnosis and risk assessment.

These examples highlight the growing clinical relevance of DNA biosensors, particularly in personalized medicine and rapid diagnostics.

Most of these factors are discussed in more detail in the cited references [Xu, et al, **2009**; Patel, et al, **2016;** Diculescu, et al, **2016;** Kharrati-Koopaee, et al, **2020;** Saylan, et al, **2021;** Hua, et al, **2022;** Lino, et al, **2022;** Stephen, et al, **2022;** Yu, et al, **2023;** Bhatia, et al, **2024;** Hemdan, et al, **2024;** Mondal, et al, **2024;** Tao, et al, **2024;** Yu, et al, **2024;** Gutiérrez-Gálvez, et al, **2025;** Lien, **2025;** Pohanka, **2025**].

4. Some Specifications of DNA Biosensors Marketed in Last Five Years

While the provided text discusses the evolution and applications of DNA biosensors, it does not specify product details or specifications of DNA biosensors marketed in the last five years. To address this query, here are examples of DNA biosensors introduced recently in clinical and commercial applications:

CRISPR-Based DNA Biosensors

- **CRISPR-Cas12/13 Diagnostic Kits**

Utilize CRISPR technology for precise detection of genetic material. These kits are highly specific, capable of detecting single nucleotide polymorphisms (SNPs), and offer results within 30 minutes. Rapid testing for infectious diseases like COVID-19 and genetic mutations.

- **Electrochemical DNA Biosensors**

Graphene-Enhanced Geno sensors incorporate graphene electrodes for increased sensitivity and signal transduction. Detect DNA concentrations as low as femtomolar levels. This offers early detection of cancer biomarker and personalized medicine.

- **Portable DNA Biosensors for Point-of-Care Testing (POCT)**

Handheld DNA Hybridization Devices are compact systems comprising of integrated microfluidics for on-site analysis. Operate with minimal sample preparation and provide results within 15–20 minutes. These devices are helpful in prenatal screening, infectious disease diagnostics, and environmental monitoring.

- **Multiplexed DNA Biosensors**

Nano-enabled Multiplex Assay Platforms are capable of detecting multiple targets simultaneously using quantum dots or gold nanoparticles for signal amplification. These devices provide comprehensive disease profiling and high-throughput drug screening.

- **Wearable DNA Biosensors**

Smart Biosensor are flexible patches embedded with DNA probes for continuous monitoring of biomarkers in sweat or saliva. These are used in cardiovascular disease risk assessment and real-time health monitoring.

These products demonstrate the advancements in DNA biosensor technology, emphasizing their role in enhancing diagnostic capabilities across medical, environmental, and industrial domains.

5. DNA Biosensor Market Share Forecasts

While exact market share data for DNA-biosensors within the nanobiosensors category is not available in the search results, I can share some relevant market insights:

a. The overall biosensors market is valued at approximately $30.0-32.31 billion in 2024-2025, with projections to reach $43.8-61.02 billion by 2030-2032, growing at a CAGR of 8.2-9.5% [BioSM-06].
b. The broader nanosensors market was valued at $901.78 million in 2025 with forecasts to reach $1,838.11 million by 2034 at a CAGR of 8.25% [BioSM-03].
c. The DNA nanotechnology market specifically was valued at $4.77 billion in 2024 and is projected to reach $25.57 billion by 2033, growing at a significantly higher CAGR of 21.50% [BioSM-04].
d. In terms of application segments, medical testing is expected to hold 40.7% of the overall biosensors market share in 2025 [BioSM-06].
e. DNA-based biosensors have notable capabilities in clinical applications, with the ability to detect biomarkers at femtomolar concentrations and genetic and cancer markers with response times ranging from minutes to hours [BioSM-04].
f. Fiber optic DNA biosensors using evanescent wave technology can achieve detection limits in the picomolar range, while DNA hybridization sensors using multi-walled carbon nanotubes can detect targets in the nanomolar range [BioSM-04].

The significantly higher growth rate of the DNA nanotechnology market (21.50% CAGR) compared to the general biosensors market (8.2-9.5% CAGR) suggests increasing adoption and market penetration of DNA-based technologies, but the specific market share of DNA-biosensors within the nanobiosensors category for clinical applications is not specified in the provided search results.

6. CONCLUSION

The evolution of biosensors, particularly DNA-based biosensors, highlights their transformative impact across diverse fields such as medical diagnostics, environmental monitoring, food safety, and forensic science. From their early inception to the integration of nanotechnology, biosensors have become indispensable tools for detecting analytes with high sensitivity, specificity, and efficiency. DNA-based biosensors have revolutionized modern diagnostics by enabling early disease detection, personalized medicine, and point-of-care testing. Their ability to detect specific DNA sequences with precision and speed makes them invaluable for identifying genetic mutations, pathogens, and disease biomarkers.

Nanotechnology has further enhanced biosensor performance by addressing limitations in sensitivity, signal transduction, and portability. The incorporation of nanomaterials like graphene, quantum dots, and nanoparticles has amplified detection capabilities while enabling miniaturization and real-time monitoring. Nano-enabled biosensors now offer multiplexed assays for simultaneous analysis of multiple targets, increasing diagnostic efficiency across various applications.

As advancements in nanotechnology continue to refine biosensor designs, these devices are poised to play an even greater role in shaping the future of diagnostics. Their integration with artificial intelligence (AI) and Internet of Things (IoT) will enable smarter platforms for real-time data analysis. DNA-based biosensors represent a promising frontier in healthcare and beyond, driving innovation toward a more precise and accessible diagnostic landscape.

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