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# Next-Generation Biosensors Based on Boron Nitride: Mechanisms, Platforms, and Future Prospects

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ABSTRACT: Boron nitride (BN) nanomaterials including nanosheets, nanotubes, and nanocrystals have emerged as promising platforms for next generation biosensing due to their unique structural, electronic, and biocompatible properties. This review presents a comprehensive overview of BN-based biosensors, highlighting their structural and physicochemical characteristics, synthesis and fabrication methods, and diverse functionalization strategies. Emphasis is placed on electrochemical, optical, and hybrid sensor platforms, detailing enzyme, DNA/aptamer, and immunosensor applications, as well as advanced techniques such as surface-enhanced Raman spectroscopy (SERS) and fluorescence-based detection. The underlying sensing mechanisms, including charge transfer, electron tunneling, adsorption kinetics, and defect-mediated interactions, are analyzed to explain their influence on sensitivity, selectivity, and response time. Challenges such as large-scale synthesis, reproducibility, and device integration are discussed, alongside opportunities for microfluidic, wearable, and AI-assisted biosensors. By summarizing current achievements and identifying future directions, this review provides a critical roadmap for developing robust, high-performance BN-based biosensors for biomedical, environmental, and point-of-care applications.

Keywords: Boron nitride nanomaterials; Biosensors; Functionalization strategies; Electrochemical and optical sensing, Biomedical applications.

## 1. INTRODUCTION

Biosensors have become vital tools for the rapid, sensitive, and selective detection of numerous biological and chemical analytes, serving key sectors such as healthcare diagnostics, environmental monitoring, food safety, and biotechnology. Traditional analytical methods (e.g., chromatography, mass spectrometry) are precise but often time-consuming, expensive, and require complex infrastructure. In contrast, biosensors through the integration of biological recognition elements (like enzymes or antibodies) with signal transducers (electrochemical or optical) provide real-time, portable, and on-site detection capabilities. The accelerating demand for point-of-care diagnostics, early disease detection, and personalized medical solutions has entrenched biosensors as cornerstones of modern analytical science [1,2]. The advent of nanomaterials has radically transformed biosensor design by enabling major improvements in sensitivity, miniaturization, and signal amplification. Materials such as carbon nanostructures, quantum dots, metal oxides, and two-dimensional (2D) sheets present high surface-to-volume ratios, tunable physical and chemical characteristics, and excellent compatibility with biomolecules all of which make them ideal for

next-generation biosensor applications [3,4]. Moreover, nanomaterial-enhanced platforms enable label-free detection, multiplexed assays, and integration with microfluidic or wearable technologies bridging the gap between laboratory-grade accuracy and real-world functionality [5].

Among nanomaterials, boron nitride (BN) has emerged as a particularly promising candidate for biosensing applications due to its exceptional combination of properties. In forms such as nanosheets (BNNS), nanotubes (BNNTs), and hexagonal BN (h-BN), BN offers chemical stability, thermal resilience, mechanical strength, and a wide bandgap while maintaining low toxicity and strong biocompatibility [6–8]. Hexagonal BN (often dubbed "white graphene") stands out for its chemical inertness and capacity for surface functionalization, distinguishing it from conventional conductive carbon-based nanomaterials [6,9]. Crucially, BN's structure can be precisely engineered at the nanoscale to introduce defects, functional groups, or alter electronic features, all of which can boost biosensor sensitivity. For instance, defect-rich BN nanosheets can enhance electron-transfer kinetics, elevating electrochemical performance. BN nanotubes (BNNTs), with their high aspect ratio and hollow tubular architecture, are excellent platforms for biomolecule immobilization while ensuring structural and chemical durability [10,11]. Moreover, BN's outstanding oxidation resistance, chemical inertia, and thermal prowess make it a durable choice for demanding sensing environments, such as in surface-enhanced Raman spectroscopy (SERS) [12].

Despite BN's compelling strengths, it remains less explored than materials like graphene or transition metal dichalcogenides (TMDs) for biosensor development. While initial studies have indicated promise across electrochemical, optical, and piezoelectric sensing modalities, scalable synthesis, experimental reproducibility, and real-time, point-of-care deployment remain significant hurdles [13]. A comprehensive, mechanistic understanding of how BN's intrinsic properties impact sensing efficacy is pivotal for advancing BN-based technologies toward clinical and commercial viability. This review aims to deliver a holistic and structured overview of BN nanomaterials in biosensing contexts. It will delve into BN's structural and physicochemical foundations, survey synthesis and functionalization strategies, and explore BN-integrated platforms spanning electrochemical, optical, quantum, and mechanical detection methods. Emphasis will be placed on operating mechanisms, performance metrics (e.g., sensitivity, limit of detection, response time), and comparative advantages over other nanomaterials [13,14]. The review will also address current limitations and anticipate future advances including wearable devices, AI-enhanced sensing, and quantum sensing technologies laying out a development roadmap for next-generation BN-based biosensor systems.

## 2. Structural and Physicochemical Properties of Boron Nitride

### 2.1. Allotropes and Crystal Structures (h-BN, c-BN, BN Nanotubes, BN Nanosheets)

Boron nitride (BN) exists in diverse forms each possessing a distinct crystalline architecture that influences its material behavior and applicability. The most stable form at ambient conditions is hexagonal BN (h-BN), also referred to as "white graphene," characterized by planar hexagonal lattices of alternating boron and nitrogen atoms held together in layers by van der Waals forces. Cubic BN (c-BN) exhibits a diamond-like sphalerite structure with $sp^3$ bonding, conferring exceptional hardness and mechanical resilience. Additionally, the less-common wurtzite BN (w-BN) mirrors lonsdaleite (hexagonal diamond) with tetrahedral coordination. From the layered h-BN, quasi-2D

BN nanosheets (BNNS) can be exfoliated offering atomically thin, planar materials with unique mechanical and thermal properties. BN nanotubes (BNNTs) cylindrical derivatives akin to carbon nanotubes typically retain an insulating character with a wide bandgap (~5.5 eV), independent of chirality or diameter. These allotropes including nanoribbons, fullerenes, and quantum dots expand the structural versatility of BN for various advanced applications.

### 2.2. Mechanical, Thermal, and Chemical Stability

BN materials are renowned for their robustness. h-BN withstands oxidation up to approximately 1000 °C in air, 1400 °C under vacuum, and up to 2850 °C in inert atmospheres, demonstrating extraordinary thermal stability. Its thermal conductivity is similarly impressive ranging between 1700–2000 $W \cdot m^{-1} \cdot K^{-1}$ on par with or exceeding graphene depending on the nanoscale form. Mechanically, BNNs (nanosheets) showcase a Young's modulus close to 0.865 TPa and fracture strength of ~70.5 GPa, both maintained across multiple layers signifying structural integrity even beyond mono- or few-layer thicknesses. c-BN stands out for its extreme hardness approx. 48 GPa though slightly less than diamond, making it valuable in wear-resistant contexts [14]. Chemically, BN exhibits high inertness. It resists attack from most acids and maintains structural integrity unless exposed to aggressive alkaline melts, positioning it as a durable choice for harsh environments.

### 2.3. Electronic and Optical Properties Relevant to Biosensors

BN allotropes are wide-bandgap insulators, typically within the 5.5–6 eV range, regardless of crystallographic form or morphology. This intrinsically insulating behavior is advantageous for biosensor platforms that require minimized background conductivity, such as electrochemical or SERS substrates. Moreover, BN's optical transparency in the UV to near-IR range, low autofluorescence, and strong UV absorbance distinguish it from carbon-based nanomaterials. For example, BN nanosheets have been reported to enhance SERS signals by orders of magnitude while avoiding spectral interference a result of their high thermal and chemical stability paired with electrical insulation.

### 2.4. Biocompatibility and Surface Functionalization Potential

BN nanomaterials demonstrate exceptional biocompatibility and low cytotoxicity. Early studies on BNNTs displayed no cytotoxic effects on kidney cells even at high concentrations (~100 mg/mL), whether unfunctionalized or coated [15]. Functional coatings such as glycodendrimer, PEI, pectin, or glycol-chitosan further improved aqueous dispersion and maintained biocompatibility across varied cell types (e.g., macrophages, endothelial cells). Furthermore, conjugation with CpG oligodeoxynucleotides enhanced cellular uptake without triggering cytotoxic responses up to 100 µg/mL. Surface functionalization of BN is versatile: noncovalent approaches (e.g., wrapping with aqueous polymers or biomolecules) retain core physicochemical properties while improving dispersibility and enabling biomolecule immobilization [16]. Covalent functionalization (e.g., via diazonium salt chemistry) introduces reactive groups such as polyaniline-like coatings enhancing compatibility with polymers or biological interfaces. These properties mechanical resilience, thermal and chemical stability, insulating character, photonic transparency, and biocompatibility coupled with functionalization flexibility make BN exceptionally promising for biosensor platforms. Its ability to serve as a stable substrate, transducer interface, or signal amplifier under challenging conditions further

underscores its potential in next-generation biosensors.

## 3. Synthesis and Fabrication of Boron Nitride Nanomaterials

### 3.1. Chemical Vapor Deposition (CVD)

Chemical vapor deposition (CVD) is a bottom-up approach widely employed to grow high-quality hexagonal BN (h-BN) films or nanosheets on substrates at elevated temperatures. Common CVD precursors include gaseous species such as $BF_3/NH_3$, $BCl_3/NH_3$, and borazine, alongside solid-state options like borazane. There are multiple variants of CVD atmospheric-pressure (APCVD), low-pressure (LPCVD), and ultra-high vacuum (UHV-CVD) each balancing factors like growth speed, layer control, and equipment complexity. LPCVD is particularly effective in producing large-area monolayer h-BN films, while APCVD tends to yield less precise multilayer coverage. Using suitable metal catalysts such as copper, nickel, platinum, or iron it is possible to suppress unwanted nucleation and promote lateral growth, leading to uniform nanoscale domains over wafer-scale areas. Pyrolytic BN (PBN), another variant akin to h-BN, is typically fabricated via CVD decomposition of boron trichloride and ammonia on graphite substrates at around 1900 °C, resulting in highly pure, chemically inert coatings suitable for high-temperature and high-stress applications. Despite its advantages such as film uniformity, controllable layer thickness, and high crystallinity CVD faces challenges related to high processing temperatures (often 900–1300 °C), substantial equipment cost, and low throughput, limiting large-scale manufacturability [17].

### 3.2. Exfoliation Methods (Mechanical, Chemical)

Top-down exfoliation techniques serve as accessible routes for producing BN nanosheets (BNNSs) from bulk h-BN. Common methods include Mechanical exfoliation, such as the "Scotch-tape" method, which yields low-defect, high-quality nanosheets but is inherently limited in scale. Ball milling offers a scalable alternative but often introduces defects and lattice damage, especially with prolonged milling times. Thermal exfoliation, which involves heating h-BN to oxidize or expand layers leading to easier separation into BNNS's without intensive sonication. Liquid-phase/chemical exfoliation, typically using polar solvents like DMF, IPA, or water under ultrasonication to weaken van der Waals interactions between layers. This method can yield $g.L^{-1}$ concentrations for dispersed suspensions useful for printed devices. Hydrothermal and sonication-assisted exfoliation, whereby h-BN is subjected to high pressure and ultrasonic cavitation in reactors, significantly improving yield (e.g., from ~0.12% to ~1.68%) and nanosheet crystallinity. Each exfoliation route provides trade-offs between quality, throughput, complexity, and environmental impact e.g., chemical routes often involve harsh reagents, whereas mechanical methods are limited by scale.

### 3.3. Hydrothermal and Solvothermal Synthesis

Hydrothermal synthesis uses elevated temperature and pressure, often in aqueous solutions, to drive exfoliation or doping of BN structures. For example, sonication-assisted hydrothermal approaches yield few-layer BNNSs with superior crystallinity and higher yield compared to sonication alone. Moreover, controlled hydrothermal processing can achieve simultaneous doping or functionalization, such as oxygen or fluorine incorporation. One study prepared thin-layered BN with O-doping using $NH_4F$ as the reactive agent achieving thinner nanosheets, altered Raman and XRD signatures, and enhanced dispersibility (evidenced by higher

zeta potential) [18]. Hydrothermal methods also facilitate doping of metals into BN lattice structures via co-processing in solvothermal or hydrothermal reactors.

### 3.4. Doping and Functionalization Strategies for Biosensor Integration

BN nanomaterials can be tailored for biosensor applications through doping and surface functionalization: Metal doping via hydrothermal routes: Transition metals such as Co or Zr can be introduced into exfoliated BNNSs using hydrothermal conditions, followed by drying steps resulting in doped BN structures with modified catalytic or magnetic properties useful for sensing or antibacterial purposes. Bi doping: Bismuth-doped BNNSs demonstrate altered electronic structures (e.g., reduced bandgap and new localized gap states), affecting optical absorption and catalytic behavior, alongside enhanced antibacterial performance against pathogens like E. coli and S. aureus. Chemical functionalization: BN surfaces can be chemically modified through covalent or non-covalent strategies. Covalent functionalization e.g., using diazonium salts or oxygen-containing groups introduces reactive moieties such as –OH or –F that enhance dispersibility and biomolecule binding. Non-covalent approaches involve wrapping BNNSs with polymers or biomolecules, improving aqueous stability without disrupting the underlying lattice [19]. These tactics make BN nanomaterials more compatible with biosensor platforms by enabling specific bioreceptor attachment, signal transduction enhancement, or improved processability.

## 4. Functionalization Approaches for Biosensing

Functionalization of boron nitride nanomaterials, particularly nanotubes (BNNTs) and nanosheets (BNNSs), is essential for enabling effective biosensing by improving biomolecule immobilization, hybrid composite formation, and sensitivity. Noncovalent wrapping with polymers or biomolecules enhances dispersion while preserving BN's intrinsic properties, whereas covalent modification introduces reactive groups for strong attachment of proteins or nanoparticles. Examples include microperoxidase-11 anchored on BNNTs for improved catalysis and glutaraldehyde-functionalized BNNTs for efficient protein loading. Hybrid architectures such as chitosan–BN films and AuNP-decorated BNNSs further boost surface area, charge transfer, and stability, enabling highly sensitive platforms like myoglobin aptasensors. Ultimately, the balance between covalent and noncovalent strategies, combined with the exploitation of BN edge defects and vacancies that enhance adsorption and electronic sensitivity, makes BN-based nanomaterials highly promising for next-generation biosensor technologies.

### 4.1. Surface Chemistry and Biomolecule Immobilization

Effective biosensor function relies heavily on immobilizing biological recognition elements (like enzymes, antibodies, DNA, or aptamers) onto a stable substrate. For BN nanomaterials especially BN nanotubes (BNNTs) and nanosheets surface chemistry plays a vital role: noncovalent methods such as polymer or biomolecule wrapping facilitate aqueous dispersion while preserving intrinsic BN properties like insulation and spectral clarity. Notably, microperoxidase-11 was noncovalently anchored on BNNTs, enhancing catalytic performance through improved electron coupling. Additionally, glutaraldehyde (GA)-functionalized BNNTs enabled effective protein immobilization via electrostatic interactions proteins such as SAV, BSA, Lyz, and IgG were successfully loaded at pH values below their isoelectric points. These protein-functionalized BNNTs held promise for developing biosensors

or simulated microtubule-like signal conduits within biological systems [20].

### 4.2. Polymer and Metal Nanoparticle Hybridization

Integrating BN with polymers or nanoparticles creates hybrid structures that can significantly boost biosensor performance. One strategy involves embedding BN within a chitosan matrix: chitosan's amine groups coordinate with BN's boron atoms, resulting in stable, flexible films even with up to 60 wt% BN loading. These composites improve stability and interfacial adhesion, which are advantageous in sensor platforms. In another example, boron nitride nanosheets were decorated with gold nanoparticles (AuNPs), forming an aptasensor platform. Thiolated DNA aptamers were then immobilized on the AuNPs/BNNS composite via Au–S chemistry, enabling sensitive and selective detection of myoglobin with a detection limit of 34.6 ng/mL. Such hybrid architectures offer large surface areas, rapid charge transfer, and scarce background noise key traits for high-performing electrochemical biosensors.

### 4.3. Covalent Vs. Non-Covalent Functionalization Methods

BN surfaces can be modified using non-covalent or covalent approaches, each with specific trade-offs. Non-covalent functionalization through polymer wrapping or biomolecule adsorption preserves the pristine structure of BN and maintains desirable properties like electrical insulation and optical clarity. For instance, water-soluble polymers can wrap around BNNTs to enhance solubility without compromising structure. Conversely, covalent functionalization uses chemical reactions to introduce reactive groups such as amines or thiols on the BN surface. These functional groups enable stronger immobilization of nanoparticles (Au, Ag, Pd, etc.) or biomolecules and can lead to robust composite biosensor structures. Patent literature notes the use of such strategies to support flexible surface chemistries and broad integration into polymers or sensing devices [21].

### 4.4. Role of Defects and Edge Sites in Enhancing Sensitivity

Edge defects and vacancies in BN nanosheets provide reactive sites that dramatically enhance adsorption and sensitivity of sensor platforms. Atomically thin BN exhibits surface conformational flexibility; when molecules adsorb on BN sheets, the nanosheets tend to conform or distort, which increases adsorption energy and efficiency improving sensing capabilities compared to bulk h-BN. Furthermore, defects in h-BN tunnel barriers can facilitate enhanced tunneling currents in vertical heterostructures, yielding charge sensitivities on par with single-electron transistors demonstrating the role of engineered defects in improving electronic detection [22].

## 5. Boron Nitride-Based Biosensor Platforms

### 5.1. Electrochemical Biosensors

#### 5.1.1. Enzyme-Based Sensors

While specific studies using enzymes on boron nitride (BN) are still emerging, the platform's high chemical stability, biocompatibility, and large surface area make it a promising material for enzyme immobilization. The strong affinity of BN nanosheets for biomolecules offers a robust scaffold for designing enzyme-based sensors with high stability and reproducibility. Baha Öndeş et al. [23] pioneered the development of enzyme-functionalized boron nitride (BN) nanosheets as a novel two-dimensional catalytic material for biosensing applications. In this innovative system, the uricase enzyme specifically

interacted with the B–N groups present on the layered structure of boron nitride, forming a stable and unique catalytic interface. To enhance stability and protect the enzyme–nanomaterial complex, the surface was coated with Nafion™. The resulting enzyme-based biosensor demonstrated remarkable analytical performance. It exhibited a broad linear detection range for uric acid, spanning from 5 to 3000 µM, with impressively low detection and quantitation limits of 0.14 µM and 0.46 µM, respectively. Beyond sensitivity, the sensor showed excellent reproducibility, high selectivity against potential interfering species, rapid response times, and long-term stability, highlighting its practical applicability. Moreover, the system displayed a low Michaelis–Menten constant (Km), indicating strong enzyme–substrate affinity and efficient catalytic activity. Importantly, the biosensor successfully quantified uric acid in commercial human serum samples, achieving high recovery rates and demonstrating its suitability for real biological matrices. The study highlighted its potential as a rapid, highly sensitive, and reliable platform for clinical uric acid monitoring. Figures provided in the study illustrate the stepwise modification of the screen-printed electrode (SPE) surface and the corresponding electrochemical detection pathway for uric acid (Fig. 1). Amperometric I–t measurements at varying uric acid concentrations (5–3000 µM) confirmed the sensor's responsiveness, with the inset emphasizing the signal behavior at lower analyte levels (Fig. 2).

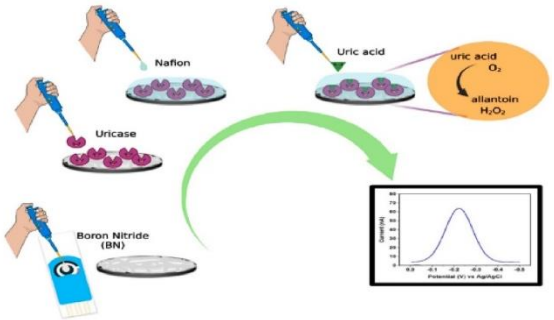


**Fig. 1. Steps for SPE surface modification and the electrochemical UA detection process [23].**

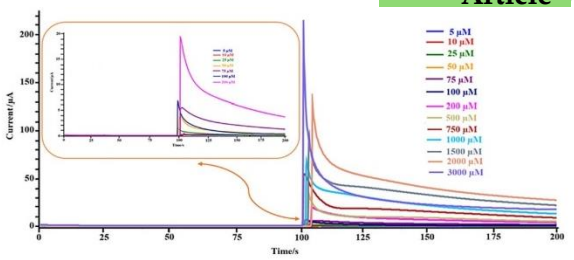


**Fig. 2. (A) Amperometric I–t curves for UA concentrations ranging from 5 to 3000 µM; inset shows responses at lower concentrations [23].**

Overall, this work establishes enzyme-modified BN nanosheets as a promising platform for next-generation biosensors, combining the advantages of two-dimensional nanomaterials with highly selective enzymatic catalysis for clinical and point-of-care applications.

### 5.1.2. DNA and Aptamer Biosensors

BN exhibits significant potential in aptamer-based electrochemical biosensing. For instance, a sensor built using colloidal BN nanocrystals and gold nanoparticles (AuNPs) immobilized on a glassy carbon electrode showed ultra-sensitive detection of the pesticide carbendazim via a DNA aptamer. The platform achieved a linear detection range from 0.1 ng/mL to 100 µg/mL and an ultra-low detection limit of 0.019 ng/mL. Moreover, porous BN frameworks combined with ATP-DNA aptamers and methylene blue fluorophores enabled detection of microbial community shifts via fluorescence. Ruijie Wang and colleagues [24] developed a highly selective electrochemical biosensor for detecting carbendazim (CBZ) by utilizing well-dispersed colloidal boron nitride (BN) nanocrystals in combination with gold nanoparticles (Au NPs). In this approach, BN nanocrystals were synthesized through a "solvent cutting" method and used to modify a glassy carbon electrode (GCE), followed by the electrodeposition of Au NPs to enhance conductivity and surface area. A single-stranded oligonucleotide labeled with methylene blue

(MB) was immobilized on the electrode via strong gold–sulfur interactions. In the presence of a specific aptamer, a double-stranded DNA structure was formed, where the aptamer chain exhibited selective binding to CBZ molecules.

Upon CBZ binding, the MB-tagged complementary strand was brought into effective contact with the electrode surface, resulting in an electrochemical signal that correlated with the CBZ concentration. Using this strategy, the sensor achieved a wide linear detection range from 0.1 ng $mL^{-1}$ to 100 µg $mL^{-1}$, with an impressively low detection limit of 0.019 ng $mL^{-1}$. The biosensor also demonstrated excellent selectivity, reliable reproducibility, and consistent performance across multiple tests. The practical applicability of the system was validated by analyzing real samples, including cucumber, kiwifruit, and water, where high recovery rates were achieved. These results confirm that the developed platform provides a robust, sensitive, and reliable method for CBZ detection in food and environmental samples.

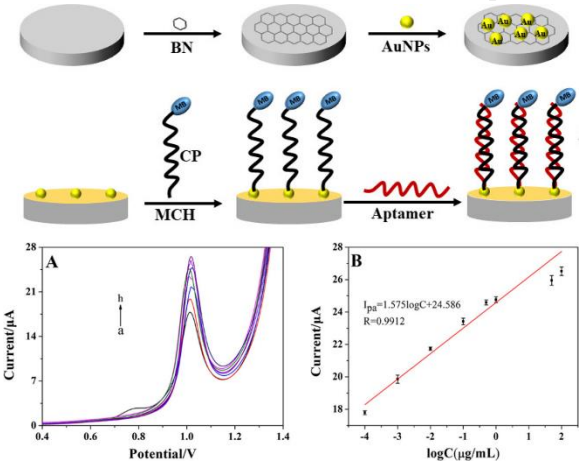


**Fig. 3. (A) DPV responses of CBZ at pH 7 on Apt/MCH/CP/AuNPs/BN/GCE for varying concentrations ((a–h): 0 to 1 × $10^{-4}$ g $mL^{-1}$). (B) Calibration curve showing the linear relationship with CBZ concentration [24].**

Figure 3 from the study illustrate the differential pulse voltammetry (DPV) responses at pH 7 for various CBZ concentrations on the Apt/MCH/CP/AuNPs/BN/GCE electrode (Fig. 6A), along with the corresponding linear calibration curve showing the correlation between MB signal enhancement and CBZ concentration (Fig. 6B). Overall, this work presents a promising electrochemical sensing strategy, combining the advantages of boron nitride nanocrystals, gold nanoparticles, and aptamer-based recognition for rapid and sensitive detection of pesticide residues.

Fengyi Wang et al. [25] reported the development of a novel photoelectrochemical (PEC) biosensor for the ultrasensitive detection of miRNA-21, leveraging a 2D–2D heterojunction composed of sulfur-doped boron nitride (S-BN) and graphitic carbon nitride (g-$C_3N_4$), combined with a dual-orbit three-dimensional (3D) bipedal DNA walker and CRISPR/Cas12a signal amplification. In this design, sulfur doping into BN enabled the formation of a 2D S-BN/g-$C_3N_4$ heterojunction, which served as a highly efficient photosensitive material to generate the initial photocurrent. A methylene blue (MB)-labeled hairpin DNA (MB-HP) functioned as the electrochemical signal probe. Upon recognition of target miRNA-21, the two swing arms of the 3D bipedal DNA walker were simultaneously activated along separate 3D orbits. This action, mediated by the Nt.BsmAI endonuclease, produced a large number of short single-stranded DNA fragments (O-DNA). These fragments subsequently triggered trans-cleavage activity of the CRISPR/Cas12a system, leading to the cleavage of MB-labeled hairpin DNA and a corresponding "signal-off" response. The biosensor demonstrated excellent analytical performance, achieving a wide linear detection range from 10 fM to 100 nM and an ultra-low detection limit of 3.98 fM (S/N = 3). Additionally, the system exhibited high specificity toward miRNA-21, making it suitable for sensitive detection even in complex samples. The rational design of this PEC platform suggests its adaptability for the detection of other nucleic acid targets or biomolecules. Figure 4 of the study

illustrates the mechanism of the PEC biosensor: (A) the construction of the 3D bipedal DNA walker and activation of the CRISPR/Cas12a system, and (B) the sequential reactions occurring on the modified electrode surface that lead to photocurrent modulation.

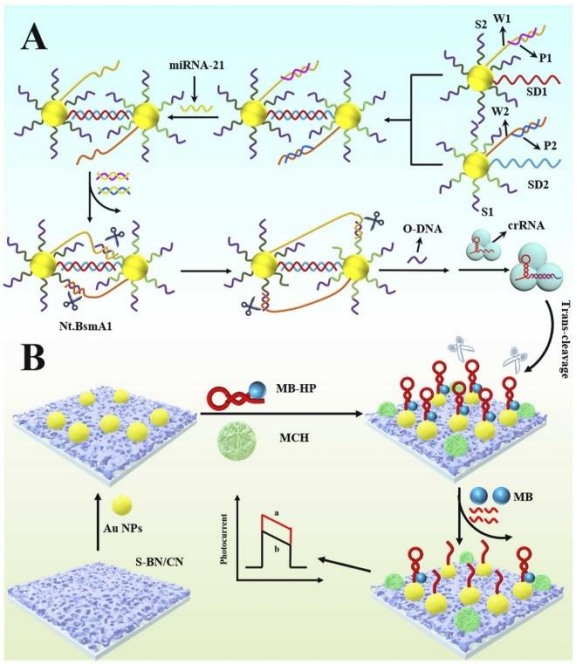


**Fig. 4. Mechanism of the PEC biosensor using a 3D bipedal DNA walker with CRISPR/Cas12a cascade signal amplification. (A) DNA walker assembly and CRISPR/Cas12a activation .principle. (B) Reaction steps on the modified electrode surface [25].**

### 5.1.3. Immunosensors

BN-based immunosensors have shown encouraging performance in detecting biomarkers. A label-free electrochemical immunosensor based on BN nanosheet-modified electrodes effectively detected cancer antigen 125 (CA125) with a detection limit of 1.18 U/mL, displaying strong selectivity, stability, and applicability in human serum matrices(PubMed, ResearchGate). Additionally, a magnetic hexagonal BN (MHBN)-based immunosensor achieved detection of T-Tau protein in artificial blood serum(ScienceDirect). BN nanosheet immunosensors have also been used successfully for carcinoembryonic antigen (CEA) detection(ScienceDirect).

Baha Öndeş et al. [26] reported the development of a novel label-free electrochemical immunosensor based on boron nitride (BN) nanosheets for the early detection of cancer antigen 125 (CA125). BN nanosheets were synthesized using a conventional sonication-assisted method and thoroughly characterized before application. These nanosheets were employed to modify the working electrode of a screen-printed electrode (SPE), providing a biocompatible platform with high surface area. The anti-CA125 antibody was directly immobilized on the BN-modified electrode surface owing to its inherent affinity for BN. To prevent nonspecific adsorption and enhance stability, the modified electrodes were blocked with bovine serum albumin (BSA) and subsequently coated with Nafion. The resulting label-free immunosensor exhibited excellent analytical performance for CA125 detection, with a linear range of 5–100 U/mL and a low detection limit of 1.18 U/mL. In addition to sensitivity, the sensor demonstrated remarkable reproducibility, selectivity, and long-term stability. Its practical applicability was validated by detecting CA125 in artificial human serum samples, even in the presence of potential interfering agents. These results suggest that the developed immunosensor holds significant potential for point-of-care diagnostics and early cancer screening. Figures in the study illustrate the stepwise surface modification of the SPE and the corresponding electrochemical detection process (Fig. 5). Differential pulse voltammetry (DPV) measurements were conducted at various CA125 concentrations (5–100 U/mL), and the calibration curve demonstrated a clear correlation between current response and antigen concentration (Fig. 6). Experimental conditions were optimized for anti-CA125 and CA125 incubation time (30 min), temperature (25 °C), and electrolyte composition

(0.1 M KCl containing 5 mM $[Fe(CN)_6]^{3-/4-}$ in pH 7.4 PBS, n = 5).

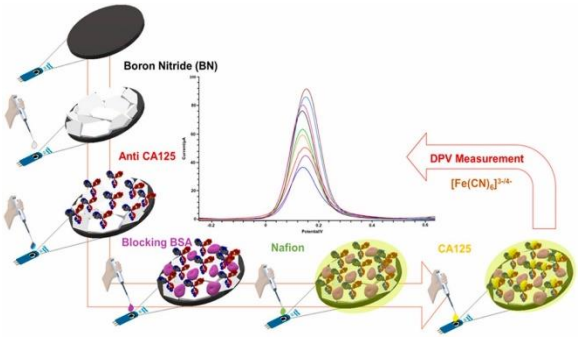


**Fig. 5. Stepwise modification of the screen-printed electrode surface and electrochemical detection procedure [26].**

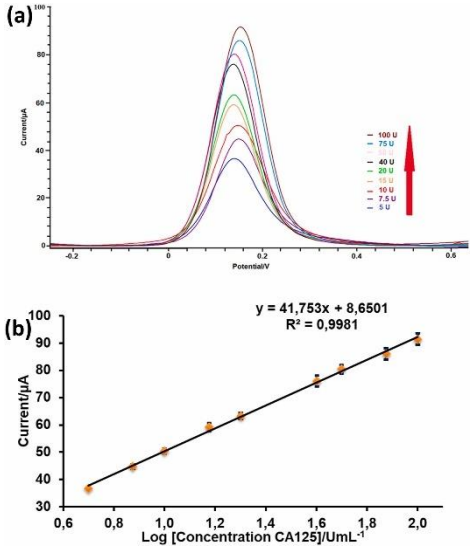


**Fig. 6. (a) DPV responses of CA125 antigen at nine concentrations (5–100 U/mL). (b) Calibration curve of current vs. CA125 concentration under optimized conditions: 30 min incubation, 25 °C, and 0.1 M KCl with 5 mM $Fe[(CN)_6]^{3-/4-}$ in pH 7.4 PBS (n = 5) [26].**

### 5.2. Optical Biosensors

#### 5.2.1. Fluorescence-Based Detection

BN materials serve as effective spacers to tune fluorescence signals. One study used few-layer h-BN as a fluorescence spacer between labeled lipid membranes to enhance signal control and specificity. Another tool leveraged porous BN with ATP-DNA aptamers and methylene blue to detect microbial redox changes by observing fluorescence shifts.

#### 5.2.2. Surface Plasmon Resonance (SPR) Sensors

Currently, there is limited evidence directly coupling BN materials with SPR biosensors. However, BN's chemical stability, optical transparency, and ability to modulate interface phenomena suggest it could function effectively as a spacer or interface layer in SPR platforms potentially enhancing signal fidelity for sensitive detection.

#### 5.2.3. Photoluminescence and Raman Sensing

qBN nanosheets enhance surface-enhanced Raman spectroscopy (SERS) performance significantly. Atomically thin BN improves Raman sensitivity by up to two orders of magnitude, offering exceptional reusability and stability as a substrate. Integrating BN with graphene and Ag nanoparticles, where BN acts as a protective spacer, synergistically boosts SERS sensitivity while minimizing photobleaching. Furthermore, h-BN phonon-polariton resonators have been demonstrated for strong coupling with molecular vibrations, showing promise for highly sensitive infrared detection platforms.

### 5.3. Piezoelectric and Microcantilever Sensors

Though explicit reports on BN-based piezoelectric or microcantilever sensors remain sparse, the inherent mechanical strength and flexibility of BN especially in nanosheet or nanotube form make it an ideal candidate. BN can be envisioned in future designs as transducing elements in piezoelectric or cantilever biosensors due to its stability and tunable mechanical properties.

### 5.4. Wearable and Implantable Biosensor Systems

To date, direct demonstrations of wearable or implantable BN-based devices are limited. However, BN's exceptional thermal and chemical resilience, biocompatibility, and inertness position it as a promising material for future wearable or implantable biosensors (Table 1). Its surface functionalization capabilities could be harnessed to develop robust, miniaturized sensors for real-time health monitoring in demanding environments.

**Table 1.** Summary Table: BN Biosensor Platforms.

| Sensor Type | BN Role | Key Examples & Performance |
|---|---|---|
| Electrochemical Aptasensor | AuNPs/BN on GCE substrate | Carbendazim detection, LOD of 0.019 ng/mL |
| Electrochemical Immunosensor | BNNS modified electrode | CA125 detection, LOD 1.18 U/mL |
| Optical Fluorescence | Fluorescence spacer or aptamer frame | Biosensing via lipid membranes / microbial activity |
| Raman (SERS) | Stable, reusable Raman substrate | Signal enhancement up to 100× |
| Infrared (SEIRA) | h-BN phonon resonator | Strong coupling detection |
| SPR (Prospective) | Spacer/interface layer | Potential for enhanced specificity |
| Piezoelectric & Wearable | Structural / interface material | Conceptual basis only, future scope |

## 6. Sensing Mechanisms and Performance Parameters

### 6.1. Charge Transfer and Electron Tunneling Phenomena

Boron nitride (BN) is inherently an insulating material with a wide bandgap (~5.5–6 eV), which limits direct electronic conduction. However, in electrochemical and hybrid devices, charge transfer can occur through electron tunneling facilitated by defects, edge sites, or conductive nanoparticle decoration. For instance, BN nanosheets decorated with gold nanoparticles (AuNPs) enable electron hopping between biomolecules and electrodes, effectively amplifying electrochemical signals in aptamer and immunosensors. Similarly, defect-rich BNNTs or few-layer BNNS can provide tunneling pathways that enhance electron transport across insulating domains, improving signal-to-noise ratios in biosensing platforms.

### 6.2. Adsorption Kinetics and Biomolecule Interaction

The sensitivity of BN-based biosensors is strongly influenced by adsorption kinetics and the interaction strength between biomolecules and BN surfaces. Atomically thin BN exhibits surface conformational flexibility, which increases adsorption energy upon biomolecule binding, leading to improved analyte capture. Surface functionalization covalent or non-covalent modulates adsorption kinetics, influencing both binding efficiency and orientation of immobilized biomolecules. Additionally, porous BN frameworks increase surface area and facilitate mass transport,

optimizing analyte access to immobilized recognition elements.

### 6.3. Sensitivity, Selectivity, Limit of Detection, and Response Time

Performance parameters of BN-based biosensors are evaluated based on sensitivity, selectivity, limit of detection (LOD), and response time. Hybrid BN platforms such as BNNS/AuNP composites demonstrate ultra-low LODs, e.g., carbendazim detection at 0.019 ng/mL (researchgate.net) and CA125 detection at 1.18 U/mL. Selectivity is often enhanced by aptamer specificity or antibody-antigen interactions, while rapid electron tunneling through conductive nanohybrids contributes to fast response times (seconds to minutes). Optical sensors leveraging BN as a spacer show minimal background interference, enhancing selectivity and dynamic detection range.

### 6.4. Reusability, Stability, and Environmental Factors

BN-based biosensors exhibit high chemical, thermal, and mechanical stability, enabling reusability and long-term performance. Atomically thin BN nanosheets resist oxidative and photobleaching degradation, allowing multiple sensing cycles with minimal signal loss. Environmental factors such as pH, ionic strength, and temperature can influence biomolecule adsorption and electron tunneling efficiency. For example, GA-functionalized BNNTs maintained protein immobilization efficiency under varied pH conditions. Robust BN platforms, especially when hybridized with polymers or nanoparticles, preserve functionality across environmental fluctuations, making them suitable for real-world, point-of-care, or wearable biosensing applications.

## 7. Challenges and Future Perspectives

### 7.1. Large-Scale Synthesis and Reproducibility Issues

One of the primary challenges for boron nitride (BN) biosensors is the scalable and reproducible synthesis of high-quality nanomaterials. Techniques like chemical vapor deposition (CVD) and hydrothermal synthesis offer precise control over BN structure but are often time-consuming, energy-intensive, and low-throughput. Exfoliation methods provide gram-scale BN nanosheets, yet they suffer from batch-to-batch variability, uneven thickness distribution, and structural defects that can affect sensor performance. Developing cost-effective, high-yield, and reproducible fabrication protocols remains critical for translating BN-based platforms from laboratory studies to industrial applications.

### 7.2. Integration with Microfluidics and Lab-on-Chip Devices

BN's exceptional thermal and chemical stability makes it promising for lab-on-chip and microfluidic biosensors, but integration presents technical challenges. BN nanosheets or nanotubes must be uniformly immobilized on microchannel surfaces without aggregation, while preserving their functional groups for biomolecule immobilization. Hybrid BN-polymer composites or patterned BN films could enhance compatibility with microfluidic substrates. Future research should focus on automated and scalable patterning techniques, as well as multimaterial integration, enabling compact, multiplexed sensing platforms.

### 7.3. Real-Time Sensing and Point-of-Care Applications

Real-time biosensing requires BN devices to maintain rapid response, high sensitivity, and stability under dynamic conditions. While BN-based electrochemical,

optical, and SERS platforms have demonstrated promising detection limits, translating these into point-of-care devices faces hurdles such as fluidic handling, signal amplification, and environmental robustness. Future work should explore self-powered sensors, wireless readout systems, and miniaturized electronics to leverage BN's advantages in portable diagnostics.

### 7.4. Regulatory and Safety Considerations for Biomedical Use

Despite BN's reported low cytotoxicity and biocompatibility, its biomedical deployment requires rigorous safety and regulatory evaluation. Issues include nanoparticle aggregation, long-term stability in physiological conditions, immunogenicity, and potential metabolic clearance. Standardized toxicity assays, in vivo studies, and regulatory compliance frameworks will be necessary before BN-based sensors can be approved for clinical applications.

### 7.5. Emerging Trends: AI-Assisted Biosensors and Wearable Healthcare Systems

BN's structural and functional versatility aligns well with emerging trends in AI-assisted biosensing and wearable healthcare systems. Machine learning algorithms can integrate BN sensor outputs for predictive diagnostics, early disease detection, and personalized health monitoring. Moreover, BN's thermal resilience, mechanical strength, and chemical inertness make it suitable for flexible, wearable, or implantable biosensors, capable of operating in harsh conditions while providing real-time physiological data. Coupling BN platforms with flexible electronics, wireless data transmission, and AI analytics is poised to transform next-generation healthcare devices.

## 8. Conclusion

### 8.1. Key Insights and Summary of Findings

Boron nitride (BN) nanomaterials including nanosheets, nanotubes, and nanocrystals demonstrate exceptional potential for biosensing applications due to their unique combination of physicochemical, electronic, and biocompatible properties. The review highlights that:

- BN's structural diversity and wide bandgap enable integration into electrochemical, optical, and hybrid biosensing platforms with minimal background interference.
- Surface functionalization, both covalent and non-covalent, enhances biomolecule immobilization, stability, and signal amplification, making BN adaptable to enzyme, DNA/aptamer, and immunosensor designs.
- BN-based hybrid systems, such as polymer or metal nanoparticle composites, improve sensitivity, selectivity, and detection limits while providing reusable and stable sensor platforms.
- The underlying sensing mechanisms including electron tunneling, adsorption kinetics, and defect-mediated interactions play critical roles in achieving ultra-sensitive and rapid analyte detection.
- Emerging device architectures, from SERS substrates to lab-on-chip and wearable sensors, demonstrate BN's versatility in addressing contemporary diagnostic challenges.

### 8.2. Outlook for Next-Generation BN-Based Biosensors

Looking ahead, BN nanomaterials are poised to transform next generation biosensing technologies:

- Overcoming scalability and reproducibility challenges will enable mass production of high-quality BN nanostructures for commercial applications.

- Integration with microfluidics, wearable electronics, and AI-assisted analytics can facilitate real-time, point-of-care diagnostics and personalized healthcare solutions.
- Continued focus on biocompatibility, regulatory compliance, and environmental stability will accelerate clinical adoption.
- Combining BN's inherent properties with emerging trends in nanotechnology and smart devices promises highly sensitive, selective, and multifunctional biosensors capable of operating in diverse biological and environmental conditions.

In conclusion, BN-based nanomaterials represent a versatile, durable, and biocompatible platform that can meet the growing demands of modern biosensing. Strategic advances in synthesis, functionalization, and device integration are expected to pave the way for innovative diagnostic tools and healthcare monitoring systems in the near future.

**Author contributions**

**Tholkappiyan Ramachandran:** Writing-original draft, Conceptualization, Writing-review and editing, Methodology, Investigation; **Ramesh Kumar Raji:** Writing-review and editing, Formal analysis, Methodology.

**Conflicts of interest**

There are no conflicts to declare.

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