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*Mini Review*

# Progress and and Developemnt Trend of Application of Bismuth-based Nanomaterials in Electrochemical Biosensors

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Bismuth is the largest nonradioactive element in the periodic table and considered to be one of the safest heavy metal elements for human beings. It is widely used in various fields due to its excellent properties. In recent years, the rapid development of electrochemical sensors has increased the demand for bismuth-based nanomaterials (BBNs) in the field of electrochemical biosensors because of their nontoxicity to organisms, good biocompatibility, and large specific surface area. However, BBNs still suffer from some disadvantages, such as poor conductivity. This problem was addressed by hybridizing BBNs with other metals to improve the electrical properties for their use in electrochemical sensors. Studies showed that BBNs could effectively improve the stability and sensitivity of electrochemical biosensors. This review introduced the preparation methods, characteristics, and application of BBNs in electrochemical biosensors, including immunosensors, enzyme sensors, and DNA sensors, followed by the characteristics of three electrochemical sensors and the performance advantages of BBNs as carriers and signal tags in developing electrochemical biosensors. Also, bismuth-based composites have been continuously explored further to improve the sensing behavior of the electrochemical biosensors. BBN-based electrochemical biosensors are predicted to be highly sensitive, convenient, selective, and stable in the future.

**Keywords:** BBNs; development trend; electrochemical biosensor; preparation method

## 1. INTRODUCTION

In recent years, various analytical methods have been applied to detect different biological analytes, such as chemiluminescence immunoassay, enzyme-linked immunosorbent assay, fluorescence immunoassay, electrochemical biosensor, and radioimmunoassay [1]. However, these

methods are often cumbersome, expensive, and time-consuming, limiting their wide applications in clinical detection. Electrochemical biosensors have attracted much attention due to their good selectivity, fast response, and low manufacturing cost. Based on their sensitivity, electrochemical biosensors are divided into electrochemical immunosensor, electrochemical enzyme sensor, electrochemical DNA sensor, electrochemical microbial sensor, and electrochemical tissue and cell sensor [2]. The continuous development of electrochemical biosensors has facilitated the improvement in the stability, sensitivity, and selectivity of electrochemical biosensors, and helped explore various nanomaterial-based electrochemical biosensors that are more convenient, easier to operate, and less expensive. Among them, the emergence of bismuth (Bi)-based nanomaterials (BBNs) has aroused great interest of researchers, showing tantalizing application prospects in the field of sensing. Compared with other nanomaterials, BBNs have been found to have more application advantages [3]{Lee, 2020 #36}.

Bi is a red to a silvery-white metal with metallic luster and weak radioactivity, and relatively stable at room temperature. Its melting and boiling points are 271.3 °C and 1560 °C ± 5°C, respectively. It can be reduced from natural metal ore in nature due to its low melting point. Bi and its compounds have gained great attention owing to their excellent properties, such as low melting point, relative stability in dry air, thermal expansion, and cold contraction during solidification, especially extremely low toxicity and excellent biocompatibility, endowing them immense use value. At present, Bi is widely used in the chemical industry, medicine, biology, and material manufacturing [4]. As BBNs are easy to be functionalized, they can be used as a signal probe *via* covalent or noncovalent interaction. For example, the doping and adsorption of some other metal particles give BBNs additional characteristics, such as electrochemical properties, magnetic properties, radioactivity, as well as various imaging and diagnostic functions. The advancements in science and technology have enabled rapid developments of BBNs in recent years, especially in biomedical and biosensor fields, because of their better biocompatibility, extremely lower toxicity, and noncarcinogenic property [5] compared with other heavy metal-based nanomaterials.

Moreover, some heavy metals form alloys, which have a wide range of cathodic potentials due to their obvious dissolution peaks [6]. Therefore, Bi was used to replace heavy metals in traditional electrochemical sensors so as to fabricate more sensitive and efficient sensors for detecting heavy metal ions, radioactive substances, and biomolecules in aqueous solutions because of their favorable electrochemical properties, good biocompatibility, chemical inertness, and high surface activity, which were conducive to the adsorption of analytes [7]. For continuous development of electrochemical sensors, particularly the electrochemical biosensors, to reach their optimum level, researchers focused on exploring electrochemical biosensors based on nanomaterials that were more convenient and sensitive, easier to operate, and less expensive, through improving their stability, sensitivity, and selectivity. Hence, in this study, the research progress of BBNs and their applications in electrochemical biosensors, including electrochemical immunosensors, electrochemical enzyme sensors, and electrochemical DNA sensors, were systematically summarized [8]. The physical and chemical properties of BBNs were first reviewed from three aspects, mainly focusing on the optimization and functionalization of BBNs: morphology change, metal doping, and surface modification. BBNs could be easily functionalized and used as a recognition unit in electrochemical

biosensors to increase the sensitivity of the sensors so as to easily miniaturize these as well as for the efficient detection of complex samples. Then, the recent research results on the electrochemical sensing application of BBNs were reviewed, where BBNs usually served as substrate materials and signal-amplifying probes to improve the electrical conductivity and electrocatalytic properties of the sensing platforms, amplify detection signals, and finally increase the sensitivity of electrochemical biosensors.

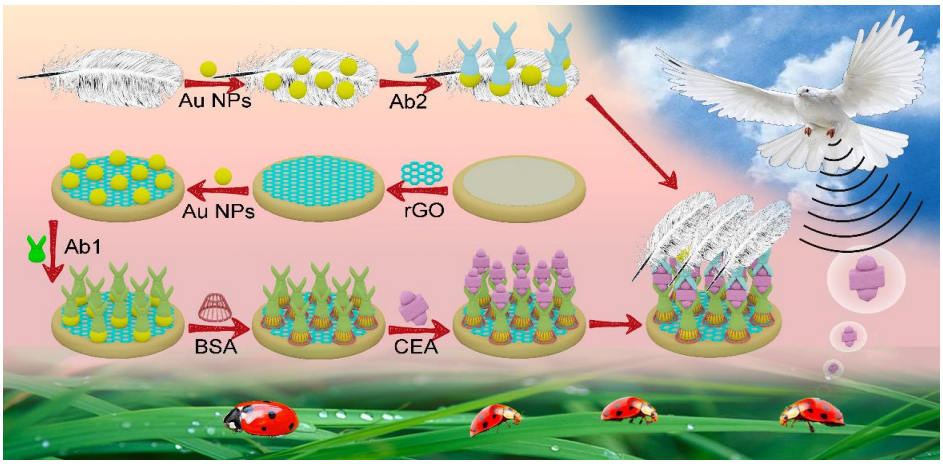


**Figure 1.** Fabrication of the Au@$CeO_2$-$Bi_2O_3$ nanofeather-based immunosensor for carcinoembryonic antigen (CEA) detection [9]. Copyright 2020 Elsevier.

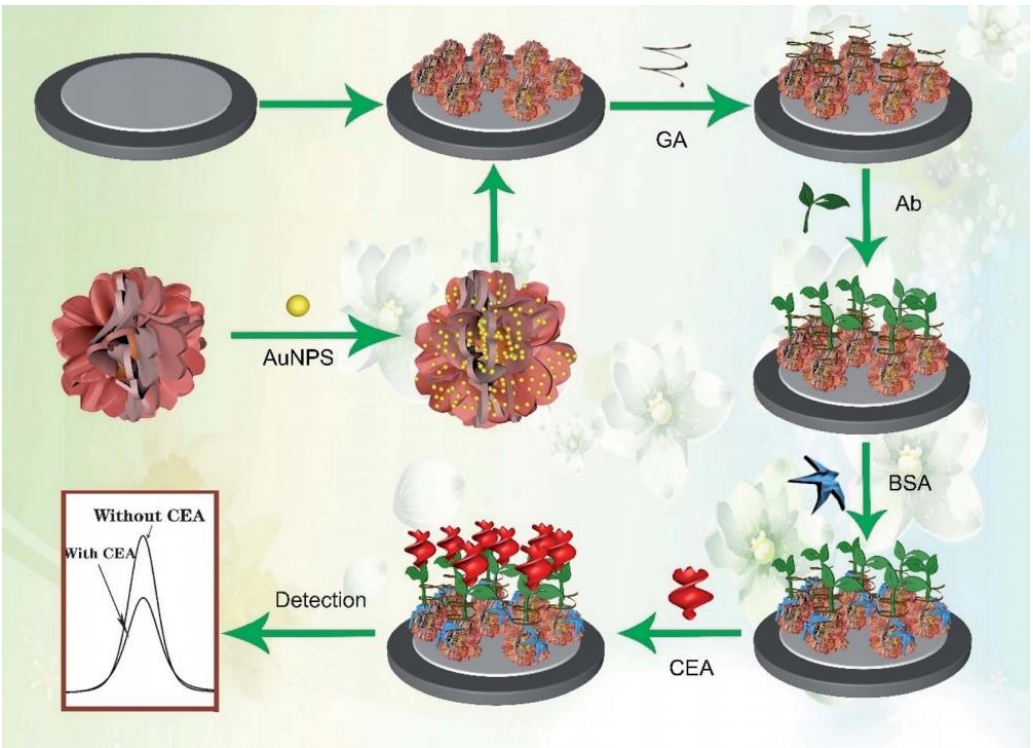


**Figure 2**. Preparation of the $Bi_2MoO_6$ nanomaterial-based electrochemical immunosensor for CEA detection [10]. Copyright 2020 Royal Society of Chemistry.

For example, the potential application of BBNs in developing various immunosensors was explored in this study. Au@$CeO_2$-$Bi_2O_3$ nanofeathers (NFs) were created as signal-amplifying probes to develop a sandwich-type immunosensor for the ultrasensitive detection of CEA. Also, the tremella-like $Bi_2MoO_6$ nanomaterials ($Bi_2MoO_6$ NTs) were synthesized and used as substrate-sensing materials to improve the efficient capture of CEA by increasing the sensitivity of the unlabeled immunosensor toward CEA detection, as shown in Figures 1 and 2 [9, 10].

## 2. FUNCTIONALIZATION OF BBNs

As mentioned in the previous section, BBNs have shown good development prospects for biosensors because of their large specific surface area and good biocompatibility, and thus have become one of the hot research directions. However, BBNs still have some nonignorable defects, such as poor electron transfer rate, low electrocatalytic performance, toxicity, hydrophobicity, chemical stability, and so on. These limitations need to be addressed by functionalizing the BBNs with an aim to make full use of their advantages and avoid the disadvantages to the greatest degree [11]. In general, this can be done in three different ways: the first method involves controlling the shapes of BBNs. The morphologies of the BBNs are controllable by adjusting the synthesis steps and changing the experimental variables so as to meet the experimental requirements. The second method involves hybridizing the BBNs with other metals [12]. Hybrid materials are composed of a variety of uniformly mixed nanolevel components, showing some improved properties compared with the two single components or some new characteristics as a result of the synergistic effect. The third method is to modify the surface of BBNs. The surface modification of BBNs is easy to be realized by changing the surface structure and morphology of BBNs mostly by chemical methods to endow BBNs with desired functions, such as improved sensing properties.

### *2.1 Morphology control*

The unique physical and chemical properties and the size of nanomaterials mainly determine their applications. Both the size and morphology of nanomaterials have a great influence on their physical and chemical properties. BBNs with small sizes often provide larger specific surface area, more active sites, hollow structures, and ordered mesopores than those with relatively larger sizes. For instance, Bi-based oxide nanostructures with unique morphology can help maintain low leaching, high loading, and good electrochemical stability and improve catalytic activity. Therefore, controlling the morphology of BBNs during the synthesis can effectively facilitate their practicability in specific applications. Generally, the morphology of BBNs can be classified into three categories: one-dimensional (1D) nanospheres; 2D nanowires, nanorods, and nanotubes; and 3D nanostructures, such as hollow nanospheres, nanoflowers, nanosheets, and feather-like and sea urchin-like nanomaterials [13]. Different morphologies can be prepared using different preparation methods. The synthesis of BBNs has tended to be simple and efficient. The one-pot hydrothermal method and the sol-gel method are mostly used to prepare BBNs to fabricate various electrochemical biosensors. Previous studies showed that the morphologies of the BBNs were effectively controlled by changing the temperature,

pH value, and reaction time during the synthesis [14, 15]. Figure 3 shows the scanning electron microscope (SEM) images of BBNs with different morphologies obtained by varying different synthesizing factors.

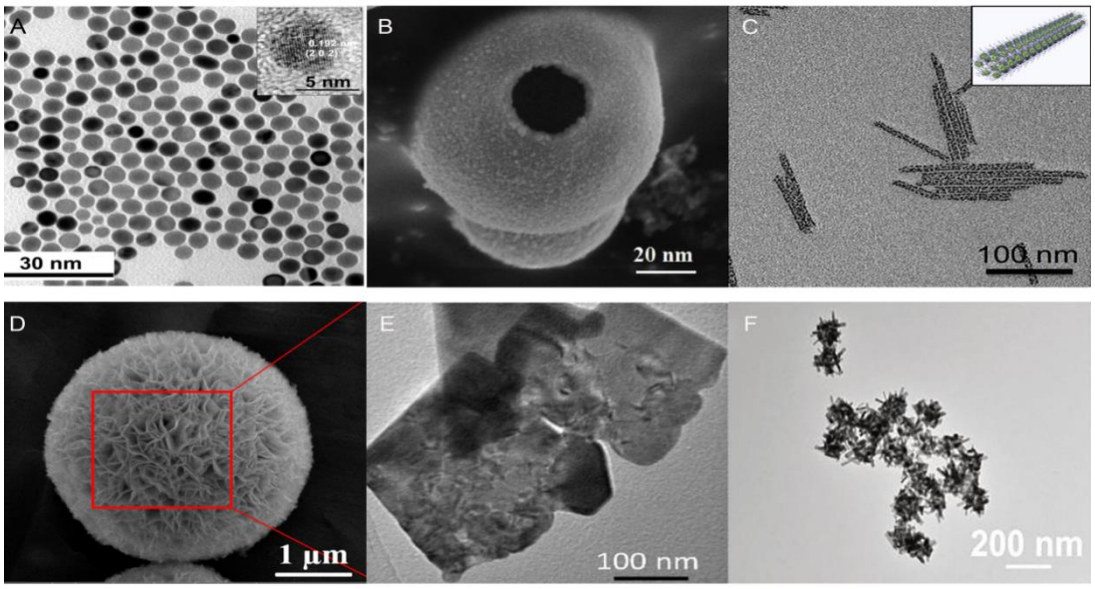


**Figure 3.** SEM images of BBNs with different morphologies [14, 16-20]. Copyright 2018 American chemical society. Copyright 2019 Elsevier. Copyright 2018 American chemical society. Copyright 2019 Elsevier. Copyright 2019 American chemical society. Copyright 2020 Elsevier.

Nanosized Bi-based materials are more suitable for electrochemical biosensors than large-scale ones because of their larger specific surface area and more active sites. The 2D BBNs, such as nanorods, nanowires, and nanotubes, have been widely synthesized by different preparation methods and used in the field of electrochemical biosensors because their unique conducive structure could be used as good electron transport channels to enhance the conductivity of the electrochemical sensing platforms [19]. For example, 2D $CuBi_2O_4$ nanosheets modified with gold were used in immunosensors as an excellent carrier of bioactive molecules, providing a basis for the successful construction of immunosensors [21]. Compared with the 2D BBNs, the 3D Bi-based nanoflowers and hollow spheres were more advantageous due to the specific surface area and catalytic activity sites [22]. For example, the 3D $BiOI/Bi_2S_3$ nanoflowers with a spatial layered structure had a larger specific surface, which provided more sites for bioactive molecules and improved the stability of the immunosensors [23]. The 3D BBNs used as carriers were found to offer more active regions for efficient biomolecule binding such as the oxidase, verifying the catalytic efficiency and great potential of BBNs in the field of electrochemical biosensors [24].

*2.2 Metal hybridization*

Noble metals and magnetic nanoparticles with high catalytic performance and ultrahigh conductivity are preferred to improve the sensitivity of the sensors so as to reduce the detection limit

and improve the detection range of the electrochemical biosensors. However, the high cost and low utilization efficiency of free precious metals, such as Pt and Pd, urged the emergence of BBNs, which had the characteristics of low cost and good biocompatibility [25], leading to a research direction to hybridize BBNs with precious metals and other metals. Such hybrid BBNs could effectively solve the problems such as the migration and aggregation of free metal nanoparticles and the quenching of catalytic active sites [26]. The introduction of BBNs reduced the cost and increased the atom utilization rate while maintaining the catalytic efficiency of the materials. The doping of other metals into BBNs could not only strengthen the electrochemical stability of Bi-based hybrid materials but also improve the biocompatibility and catalytic activity of the BBN-based biosensors, typically toward $H_2O_2$ reduction [27]. For example, the cubic Pt/Bi hybrid nanomaterials could protect the metal composites from agglomeration by doping Pt into BBNs, showing good chemical and electrical stability. Also, doping minimized the size of cubic Pt/Bi alloys, enlarged specific surface area, enhanced the catalytic performance, and increased the metal utilization rate [3].

### *2.3 Surface modification*

Surface modification refers to changing the surface state and morphology of the materials by physical or chemical methods. The stability and electrochemical properties of the modified BBNs could thus be improved as expected. BBNs have been modified with other metal nanoparticles, such as Au, Pt, Ag, or some polymers such as polyvinylpyrrolidone, to change their size, stability, and biocompatibility. The response signal of the BBN-based biosensors could be amplified through surface modifications, resulting in enhanced detection performance, particularly the sensitivity of the sensor [28]. The surface modification of BBNs with polymers has been one of the most popular methods of surface modification, including polyethylene glycol, polyetherimide, and 3-aminopropyl triethoxysilane [29], which could graft various functional groups to the surface of BBNs, such as amino and thiol groups. As for the amino group, strong coordination bonds could be formed with most of the empty orbitals due to the existence of lone pair of electrons [30].

Among various surface modification methods, the most popular trend has been modifying the surface of BBNs with precious metals. BBNs with large specific surface areas have become an excellent carrier of some precious metals. Mesoporous or porous BBNs were synthesized with precious metals grown inside, which greatly improved the overall electrochemical properties of the materials, avoiding the high cost and low utilization of precious metals. Modifying BBNs with catalytic properties has become a research trend toward increasing the sensitivity of the sensor. As reported, the mesoporous BiPt nitrophenols (NPs) greatly improved the electrocatalytic performance of the sensor toward the reduction of hydrogen peroxide to oxygen (Fig. 4). Therefore, modifying the surface of BBNs is of great significance to improve the properties of BBNs [31].

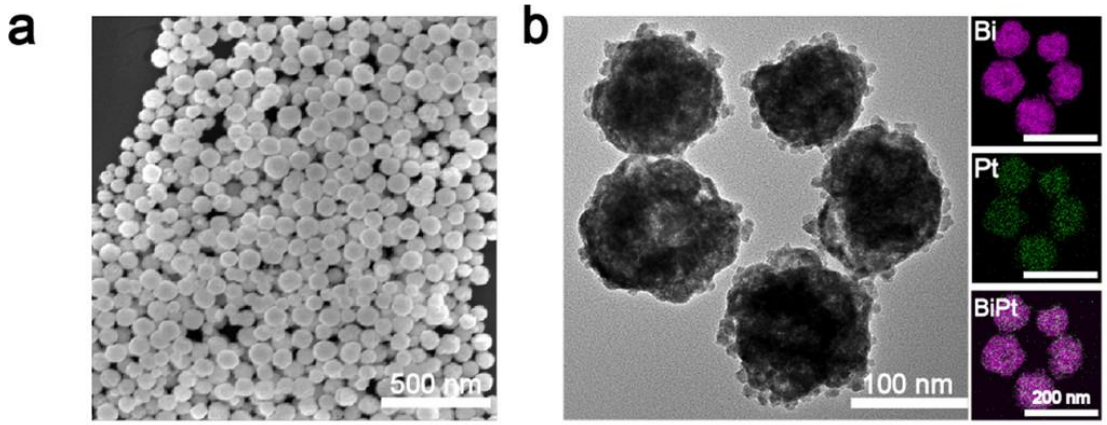


**Figure 4.** Characterization of BiPt NPs. (a) SEM image. (b) Transmission electron microscopy image and the energy dispersive x-ray spectroscopy elemental mappings [31]. Copyright 2020 American chemical society.

## 3. APPLICATION OF BBNs IN ELECTROCHEMICAL BIOSENSORS

### *3.1 BBN-based electrochemical immunosensors*

The electrochemical signals generated due to the interaction between the antigen (Ag) and antibody (Ab) are usually captured for detection using electrochemical immunosensors. Ag, including pathogens, bacteria, and so on, can produce specific immune responses due to the immunogenicity and combine with Ab because of the immune reactivity [32]. The Ab is a kind of immunoglobulin produced by Ag eroding living cells, which is used to fight against the Ag. Immunosensors are of two kinds: sandwich immunosensor and unlabeled immunosensor [33]. A sandwich immunosensor is usually a specific Ab or Ag labeled with an enzyme. The common method involves directly fixing Ab or Ag to the electrode with amplified signal material, which combines with the specific substance to be measured, resulting in the change in potential and response signals. The electrochemical immunosensor has the advantages of high stability, high specificity, low cost, high efficiency, and short detection cycle, and is easy to carry. It has been widely used in clinical medicine, environmental monitoring, food testing, customs, and other fields. According to different detection signals, electrochemical immunosensors can be divided into potential immunosensor, current immunosensor, conductance immunosensor, and capacitive immunosensor. Immunosensors have unique recognition and binding functions toward the corresponding Ags by Abs; they can be divided into direct and indirect types [20].

#### *3.1.1 Unlabeled immunosensors*

In traditional electrochemical sensors, BBNs lead to poor electrical signals because of their poor electronic transmission ability. However, in recent years, some researches on low fiber

nanostructures are in progress [34]. Bi and its compounds have become the characteristics of current research due to their unique structures and properties, such as highly anisotropic Fermi surface, high refractive index, dielectric constant, and low carrier density. Bi oxide ($Bi_2O_3$)-related nanomaterials as solid electrolytes have good properties. For example, the $Bi_2O_3$ nanorod bundles with long cubic fiber structures provide higher specific surface area, thus enhancing the load of Ab and providing good conditions for constructing immunosensors [35, 18]. Figure 5 shows the SEM of $Bi_2O_3$ nanorods with a long cubic fiber structure.

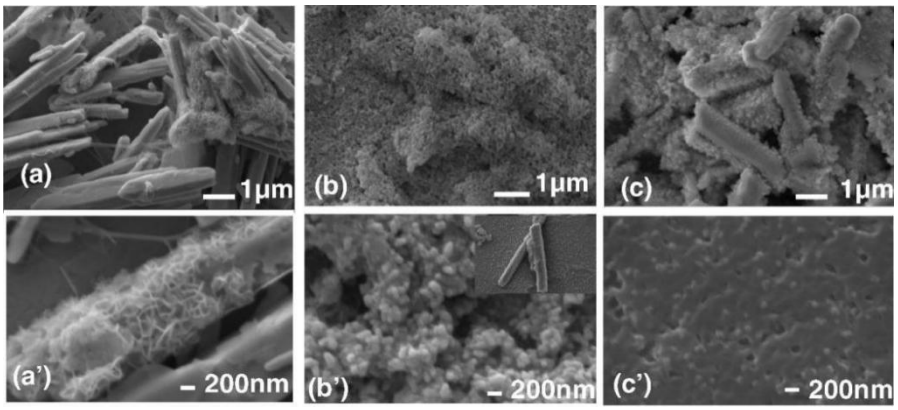


**Figure 5.** SEM images of $Bi_2O_3$ nanorods with long cubic fiber structure [11]. Copyright 2017 Elsevier.

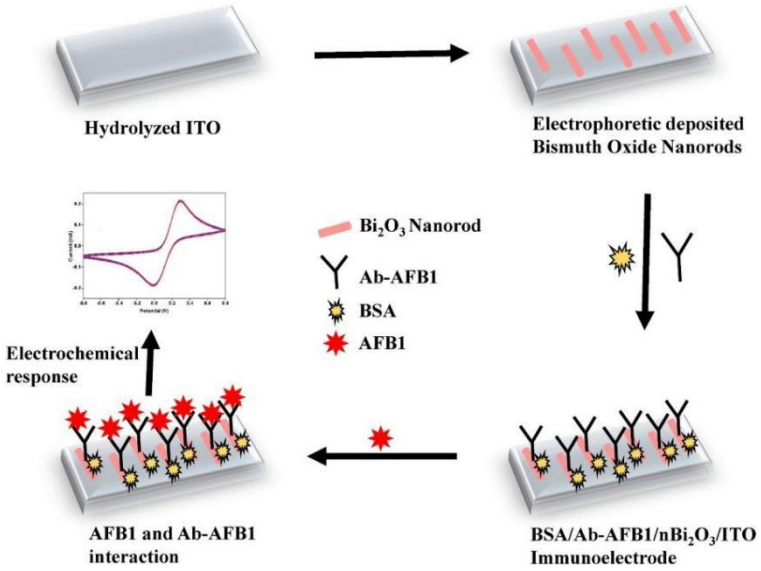


**Figure 6.** Schematic preparation process of BBN-based immunosensors [11]. Copyright 2017 Elsevier.

Figure 6 shows the step-by-step fabrication process of Ab- n$Bi_2O_3$/indium tin oxide (ITO) on the surface of the $Bi_2O_3$/ITO electrode. First, $Bi_2O_3$ was immobilized on the ITO electrode, and then the Ab was dispersed in phosphate buffer saline (PBS) and dropped onto the surface of the electrode. As the $Bi_2O_3$NPs were positively charged, the carboxyl group of Ab-AFB1 was negatively charged. In this way, the Ab could be bound to the material by electrostatic interaction, and bull serum albumin (BSA) solution could seal the specific sites that were not bound. The adsorbed Ab still retained its biological activity because of the good biocompatibility and nontoxicity of BBNs.

In recent years, $Bi_2O_3$ nanofilm composites were used in biosensors for detecting phenolic compounds. $Bi_2O_3$ and chitosan composite nanomaterials were used to prepare electrochemical DNA biosensors. $Bi_2O_3$ NP-doped multiwalled carbon nanotube (MWCNT) nanocomposites with high conductivity were dripped onto glassy carbon electrodes (GCEs) to catalyze the detection of hydrogen peroxide. Lithium-doped $Bi_2O_3$/MWCNT-modified GCEs were applied to monitor the electrocatalytic behavior of ascorbic acid. The possibility of using BBNs in electrochemical immunosensors still has a great exploration space due to the various characteristics of BBNs[36]. With the emergence of new pathogens, it is important to explore different electrochemical immunosensor detection methods. Researchers must develop different ways to test new pathogens. In fact, BBNs have many excellent properties compared with other metal materials, so the application of BBNs in electrochemical immunosensors has great prospects [16, 37].

At the same time, BBNs could also be used as modifiers and internal reference materials to make a ratiometric electrochemical immunosensor for detecting various tumor markers. This ratiometric method was used for multiple detection of cancer cell markers and had a low detection limit, good consistency, repeatability, and stability. Therefore, this method could be easily applied to detect other tumor markers. In addition, Bi has also been used as a point signal intensifier because the metal ions on the surface of the electrode could form binary or multielement “fusible” alloys with Bi, where the stripping peak ratio of Bi film was measured as a reference [38]. A stable anodic stripping voltammetric (ASV) current peak could thus be displayed in the ASV voltage diagram by Bi plating on multiple sensor annunciator-CNT-ATA/GCE composite electrode [39].

### *3.1.2 Sandwich-type immunosensors*

Sandwich-type immunosensors, also known as labeled immunosensors, usually use enzymes and other substances for specific labeling, Ag-Ab specific binding, and detection by electrochemical methods. At the same time, the linear relationship between the concentration of the substance to be tested and the current is obtained so as to achieve highly sensitive detection of the detection targets. BBNs are widely used in sandwich-type immunosensors because of their excellent chemical properties, such as good biocompatibility, nontoxicity, high biomolecular adsorption, and photocatalytic performance [27]. For example, $Bi_2WO_6$/$Bi_2S_3$ was prepared as a sandwich-type immunosensing platform by doping $Bi_2S_3$ into layered $Bi_2WO_6$, showing good catalytic performance toward $H_2O_2$ (hydrogen peroxide) (Fig. 7). The heterojunction formed by coupling two different semiconductors remarkably improved the sensitivity and anti-interference behavior of the designed immunosensor during the detection of COVID-19 virus in actual samples [40].

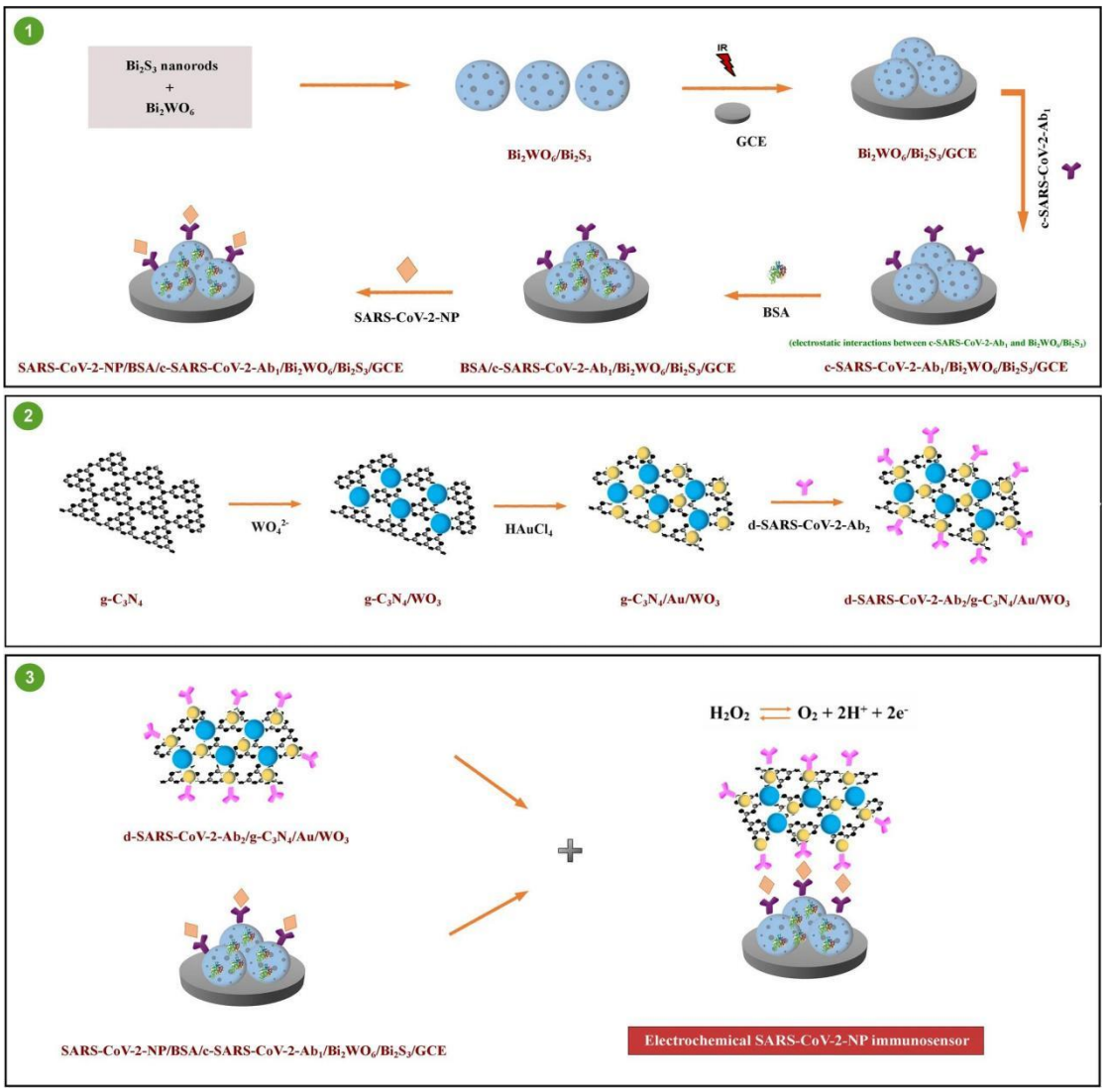


**Figure 7.** Schematic illustration of the fabrication procedure of electrochemical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunosensor [40]. Copyright 2021 Springer nature.

### *3.2 Enzyme sensors*

An electrochemical enzyme sensor captures the electrochemical signal converted from the enzyme reaction on the enzyme membrane so as to determine the concentration of active substances. The working principle is that the analyte penetrates the enzyme layer to participate in the reaction, and the concentration of an electroactive substance is detected by the potential or current sensor [41]. The electrochemical enzyme biosensor has the advantages of good catalytic efficiency, good stability, strong selectivity, specific recognition, less dosage, and convenient operation [42]. Enzyme immobilization is the key and a common method to develop enzyme sensors, which includes the Langmuir-Blodgett thin layer, conductive polymer, and so on. Among them, glucose oxidase and horseradish peroxidase are commonly used. However, the stability of the enzyme is poor. With the

increase in the number of patients with diabetes, the development of an efficient, accurate, and short-cycle sensor for measuring glucose is essential [43]. As Bi and its compounds have good biocompatibility and biomolecular adsorption, BBNs as substrate materials have a larger specific surface area, provide more active sites, and can be combined with other high catalytic performance materials to form new materials with excellent catalytic performance (called bionic enzyme) and better biocompatibility, and retain the biological activity of immobilized enzymes to a great extent. For example, the application potential of glucose enzyme-based sensors is usually 0.8 V. If the applied potential is too high, other electroactive substances interfere with the enzyme sensing, reducing the specificity of enzyme sensing and leading to poor selectivity. Therefore, novel BBNs are chosen as substrates to reduce the application potential and improve the selectivity of enzyme sensors. In the latest research, semiconductor BBNs showed great potential in preparing enzyme sensors. For example, the semiconductor BiOX (X is from the halogen family) displayed excellent optical and electrochemical properties. Figure 8 shows the multicavity ZnO/BiOI nanotube prepared on Ni foam, and the glucose oxidase was fixed within BBNs as an enzyme-loaded substrate for efficient glucose detection [44].

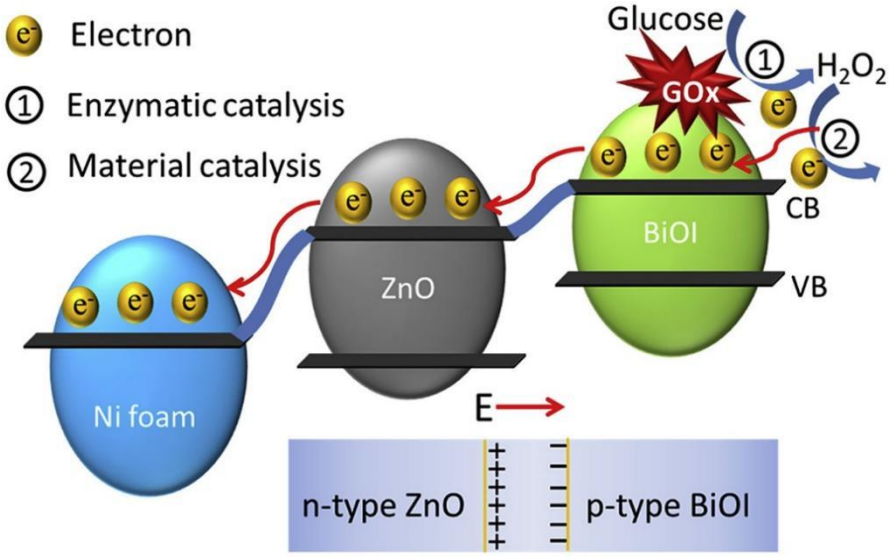


**Figure 8.** Preparation of Bi-based enzyme sensor [44]. Copyright 2020 Elsevier.

The sensitivity and current response of the amperometric enzyme sensors could be improved using novel BBNs with more active sites. Generally, the active sites of enzyme sensors for glucose detection include two aspects: one is the catalytic effect of GOx toward glucose commonly used for detection, and the other is the catalytic effect of materials modified on the electrode surface toward hydrogen peroxide. Therefore, the combination of n-type semiconductor ZnO and p-type semiconductor BiOI can be used as an enzyme-loading substrate to catalyze hydrogen peroxide for

signal amplification. Semiconductor BBNs of this kind have been widely studied due to their unique crystal structure and electron transfer mode. For example, bismuth titanate ($Bi_4Ti_3O_{12}$) as an n-type semiconductor could be rapidly prepared by one-pot hydrothermal method, producing $Bi_4Ti_3O_{12}$ nanomaterials, which could be directly grown on the titanium foil electrode. The obtained BBNs could easily be bonded to the electrode without chitosan and other binders. Bi-based semiconductors synthesized by the new method were directly grown on the electrode, which was a breakthrough for enzyme sensors and greatly improved the sensing performance of enzyme sensors [45].

Figure 9 shows a schematic diagram of the band structure of n-p $NiO/Bi_4Ti_3O_{12}$ and the electron-hole pair separation [41]. The excellent catalytic activity of the enzyme sensor could be achieved by the heterogeneous junction formed through the combination of n-type semiconductor with p-type semiconductor. Based on the theory of the electric double layer, the combination of two semiconductor materials formed an internal electric field at the interface. The negative p-zone and the positively charged n-zone generated electron-hole pairs under the formation of the electric field. The internal electric field could improve the electron mobility and separation efficiency of the electron-hole pair, thus improving the sensing performance.

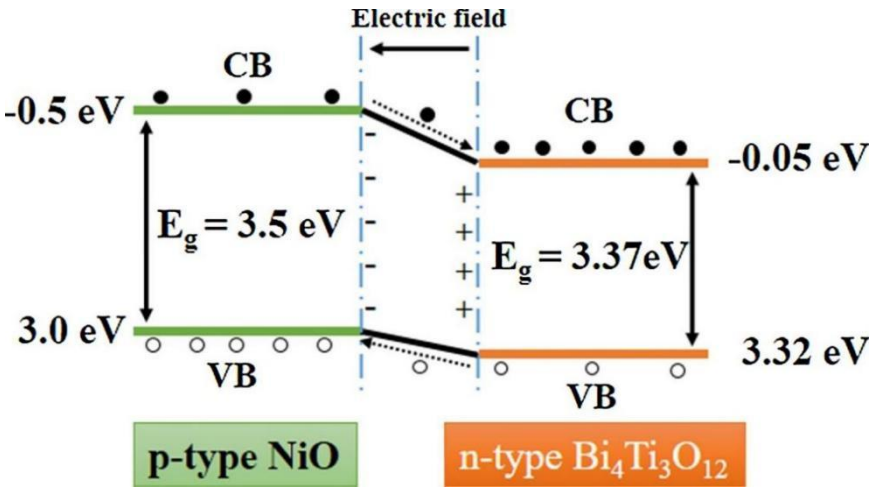


**Figure 9.** Schematic diagram of the band structure and electron-hole pair separation of $NiO/Bi_4Ti_3O_{12}$ [41]. Copyright 2018 Elsevier.

*3.3 DNA sensor*

The electrochemical DNA sensor converts the target DNA into an electrochemical signal for detection. The sensor uses nucleic acid as a molecular recognition element, namely DNA probe, to identify the presence of target DNA in the sample to be tested. The hybridization between the probe and the target DNA is expressed in the form of an electrochemical signal using a transducer. DNA sensor has great application in medical, biological, and electronic technology. DNA double-strand-specific hybridization increases the specificity of the sensor because of its strong specificity. Compared with traditional gene detection methods such as optical biosensors, chromatographic methods such as ultra-high-performance liquid chromatography spectrum and lateral flow

immunochromatography have been reported [46]. The electrochemical DNA sensors have the characteristics of being fast, sensitive, simple, and low cost. Nowadays, BBNs have shown great potential as signal probes for signal amplification for the development of labeled DNA sensors due to their excellent electrochemical stability and electrocatalytic properties, good biocompatibility, and low cost compared with the unlabeled DNA sensors.

The preparation of BBN-based DNA sensors has become a trend for the catalytic activity toward peroxides. The prepared BBNs have the advantages of large specific surface area and good electrocatalytic performance, which can be used as the carrier of DNA sensor aptamer for signal amplification and accurate detection of the detected substances. For example, an electrochemical DNA sensor was constructed by combining $BiVO_4$ with a highly selective aptamer to detect β-lactoglobulin (β-LG). As shown in Figure 10, the highly selective aptamer ensured the selectivity of the DNA sensor, while the $BiVO_4$ with high catalytic performance significantly increased the sensitivity of the sensor toward DNA detection.

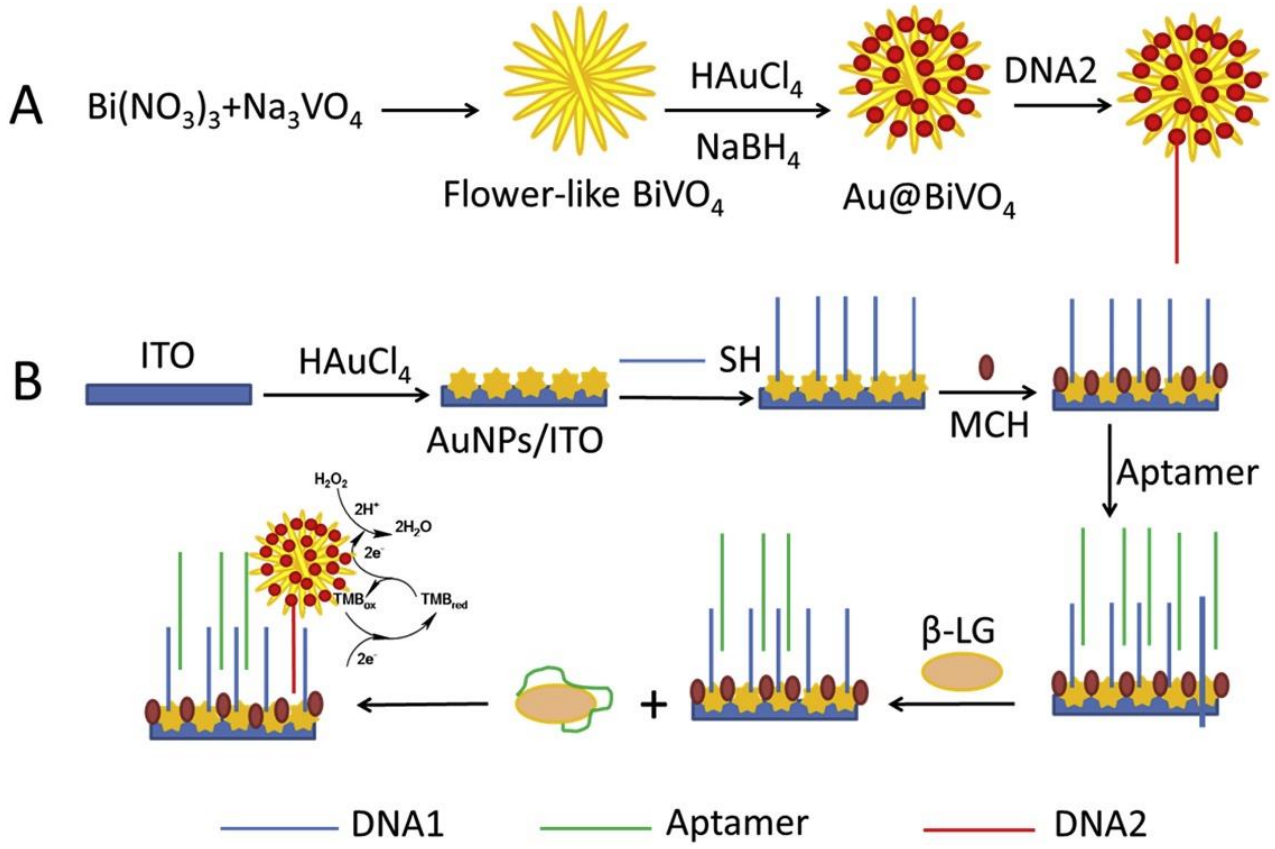


**Figure 10.** Preparation of Bi-based DNA sensor [26]. Copyright 2020 Elsevier.

The synthesis of BBNs with better performance for DNA sensors has become popular to obtain a lower detection limit so that BBNs can better combine with DNA amplification technology. It was found that $Bi_2Se_3$ nanosheets could be loaded and aggregated with more Au NPs, and the sensitivity of

the sensor could be improved by the covalent bonding of amino and Au NPs with more signal probes. As shown in Figure 11, the capture unit, signal unit, and target DNA formed a sandwich-type DNA sensor. The signal probe was fixed on the BBNs to reduce 4-NP. The newly prepared BBNs effectively improved the current signal by increasing the activity of the peroxide [12].

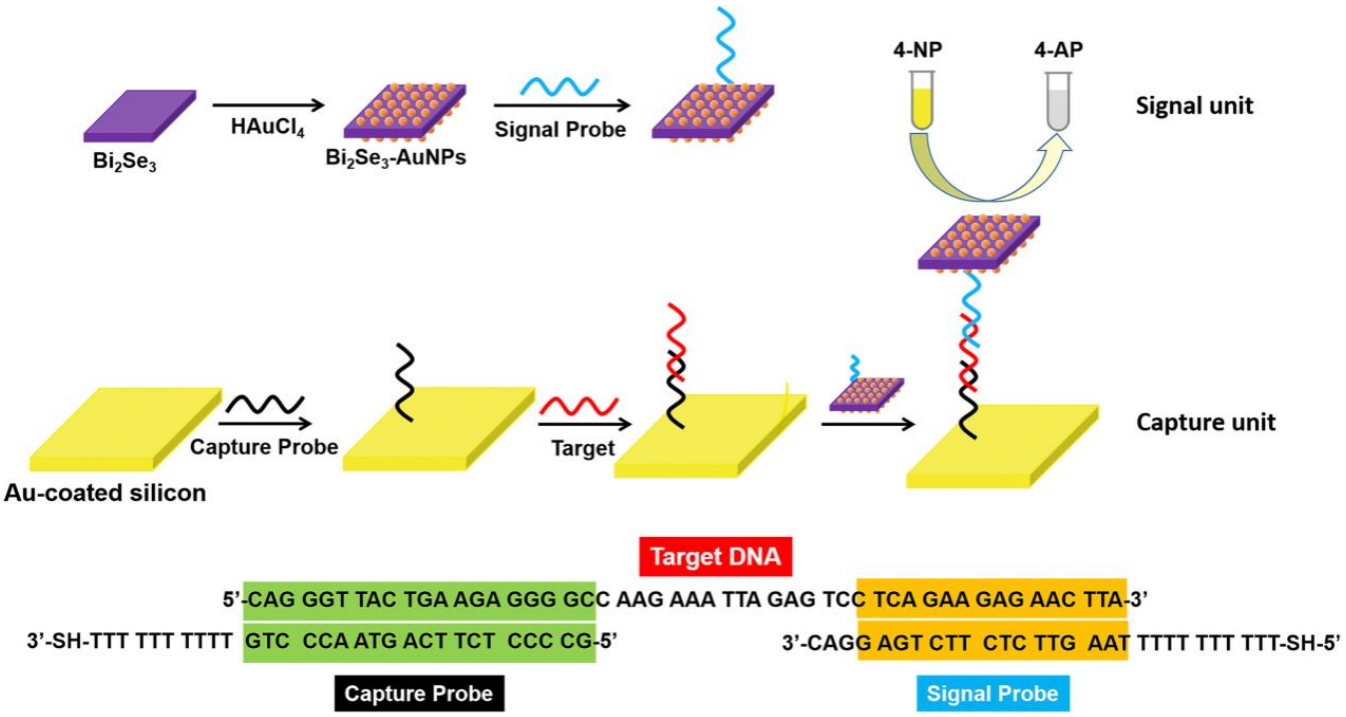


**Figure 11.** Detection principle of the colorimetric sandwich-type biosensor [39]. Copyright 2020 Elsevier.

Compared with the flaky $Bi_2Se_3$, the synthesized $Bi_2Se_3$ NPs have been also applied to fabricate DNA sensors. The $Bi_2Se_3$ NPs, as signal-amplifying agents between gold electrodes and electrodeposited gold, showed excellent signal amplification effect during the electrochemical test of DNA. As shown in Figure 12, the electrodeposition of gold on the surface of $Bi_2Se_3$ NPs ($Bi_2Se_3$@Au) further improved the stability of BBNs and retained the catalytic and electrochemical properties of $Bi_2Se_3$ NPs.

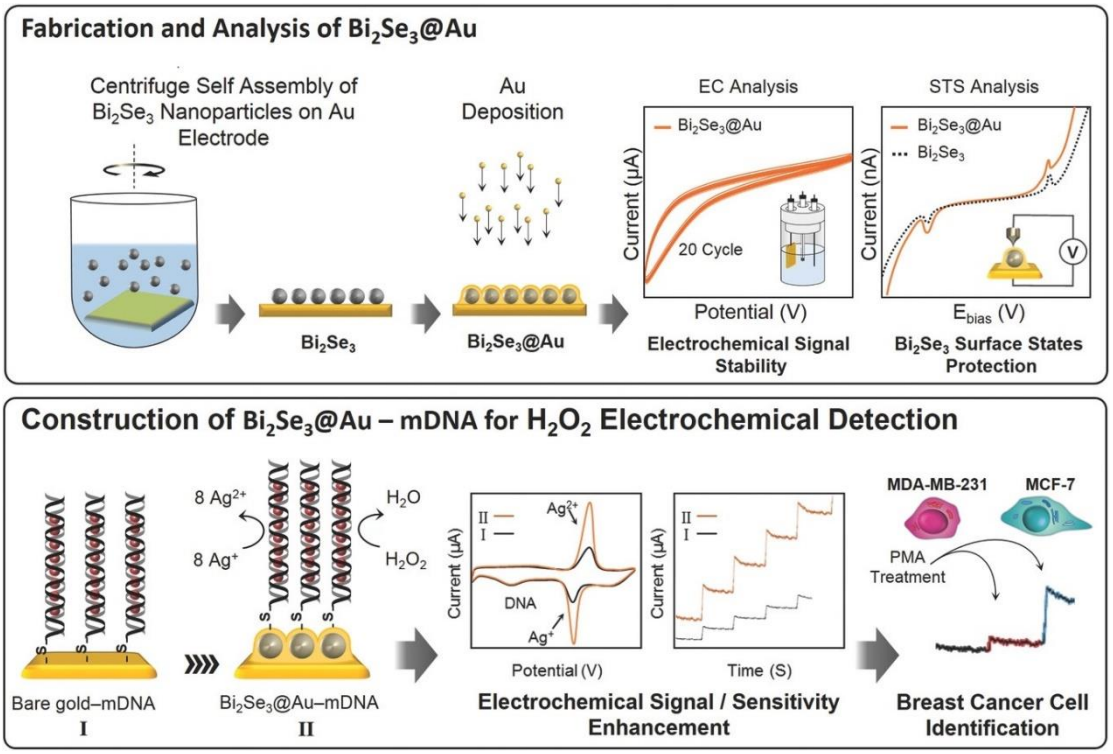


**Figure 12.** Schematic diagram of the fabrication process of $Bi_2Se_3$@Au-mDNA electrode [12]. Copyright 2018 John Wiley and Sons.

## 4. CONCLUSION AND PROSPECTS

In conclusion, this review mainly introduced the application and the development trend of BBNs in different electrochemical sensors. The properties of BBNs could be improved through morphology control, surface modification, and metal hybridization. The characteristics and research progress of BBNs in three kinds of electrochemical biosensors, their construction methods, and detection principles were reviewed, followed by their advantages in electrochemical biosensors. The good biocompatibility and the large active sites of BBNs made BBNs suitable and preferred to be used as a carrier for loading various biomolecules, leading to excellent performance in electrochemical sensors, providing the possibility for subsequent applications in practical samples. Therefore, it has become a potential trend to explore further the application of various new BBNs in electrochemical biosensors to solve current practical problems.

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**References**


1. *C. Fu*, Y. Sun, C. Huang, F. Wang, N. Li, L. Zhang, S. Ge, J. Yu, *Talanta*, 223 (2021) 121719.
2. D. Song, J. Zheng, N.V. Myung, J. Xu and M. Zhang, *Talanta*, 225 (2021) 122006.
3. H. Lee, Y. Sohn and C.K. Rhee, *Langmuir*, 36 (2020) 5359.
4. Y. Feng, Q. Shao, F. Lv, L. Bu, J. Guo, S. Guo and X. Huang, *Adv. Sci.*, 7 (2019) 1800178.
5. E. Ma, P. Wang, Q. Yang, H. Yu, F. Pei, Y. Zheng, Q. Liu, Y. Dong and Y. Li, *ACS Biomater. Sci. Eng.*, 6 (2020) 1418.
6. Y. Jia, Y. Li, S. Zhang, P. Wang, Q. Liu and Y. Dong, *Biosens. Bioelectron.*, 149 (2020) 111842.
7. Y. Lai, L. Wang, Y. Liu, G. Yang, C. Tang, Y. Deng and S. Li, *J. Biomed. Nanotechnol.*, 14 (2018) 44.
8. F. Li, J. Feng, Z. Gao, L. Shi, D. Wu, B. Du and Q. Wei, *ACS Appl. Mater. Interfaces*, 11 (2019) 8945.
9. X. Tian, P. Cao, D. Sun, Z. Wang, M. Ding, X. Yang, Y. Li, R. Ouyang and Y. Miao, *Appl. Surf. Sci.*, 528 (2020) 146956.
10. Z. Wang, X. Tian, D. Sun, P. Cao, M. Ding, Y. Li, N. Guo, R. Ouyang and Y. Miao, *RSC Adv.*, 10 (2020) 15870.
11. P.R. Solanki, J. Singh, B. Rupavali, S. Tiwari and B.D. Malhotra, *Mater. Sci. Eng. C Mater. Biol. Appl.*, 70 (2017) 564.
12. M. Mohammadniaei, J. Yoon, T. Lee, B.G. Bharate, J. Jo, D. Lee and J.W. Choi, *Small*, 14 (2018) 1703970.
13. T.R. Das and P.K. Sharma, *Microchem. J.*, 147 (2019) 1203.
14. D. Fan, C. Bao, X. Liu, J. Feng, D. Wu, H. Ma, H. Wang, Q. Wei and B. Du, *Talanta*, 198 (2019) 417.
15. Y. Liu, Y. Zheng, Z. Chen, Y. Qin and R. Guo, *Small*, 15 (2019) 1804987.
16. X. Hu, J. Sun, F. Li, R. Li, J. Wu, J. He, N. Wang, J. Liu, S. Wang, F. Zhou, X. Sun, D. Kim, T. Hyeon and D. Ling, *Nano. Lett.*, 18 (2018) 1196.
17. W.N. Wang, P. Pei, Z.Y. Chu, B.J. Chen, H.S. Qian, Z.B. Zha, W. Zhou, T. Liu, M. Shao and H. Wang, *Chem. Eng. J.*, 397 (2020) 125448.
18. Y. Zang, L. Gong, L. Mei, Z. Gu and Q. Wang, *ACS Appl. Mater. Interfaces*, 11 (2019) 18942.
19. Z. Zeng, S. Fang, D. Tang, R. Xiao, L. Tang, B. Peng, J. Gong, B. Long, X. Ouyang and G. Zeng, *Microporous Mesoporous Mater.*, 284 (2019) 177.
20. C. Zhang, J. Ren, J. Hua, L. Xia, J. He, D. Huo and Y. Hu, *ACS Appl. Mater. Interfaces*, 10 (2018) 1132.
21. G.C. Fan, S. Gu, D. Zhang, Z. Hu and X. Luo, *Biosens. Bioelectron.*, 168 (2020) 112563.
22. S.Y. Yu, L. Zhang, L.B. Zhu, Y. Gao, G.C. Fan, D.M. Han, G. Chen and W.W. Zhao, *Coord. Chem. Rev.*, 393 (2019) 9.
23. S. Zhang, C. Wang, T. Wu, D. Fan, L. Hu, H. Wang, Q. Wei and D. Wua, *Biosens. Bioelectron.*, 196 (2022) 113703.
24. L. Yu, X. Cui, H. Li, J. Lu, Q. Kang and D. Shen, *Analyst*, 144 (2019) 4073.
25. Q. Yang, N. Li, Q. Li, S. Chen, H.L. Wang and H. Yang, *Anal. Chim. Acta*, 1078 (2019) 161.
26. S. Xu, B. Dai, W. Zhao, L. Jiang and H. Huang, *Anal. Chim. Acta*, 1120 (2020) 1.
27. M. Li, P. Wang, F. Li, Q. Chu, Y. Li and Y. Dong, *Biosens. Bioelectron.*, 87 (2017) 752.
28. Y. Li, L. Liu, X. Liu, Y. Ren, K. Xu, N. Zhang, X. Sun, X. Yang, X. Ren and Q. Wei, *Biosens. Bioelectron.*, 163 (2020) 112280.
29. A. Muthumariyappan, U. Rajaji, S.M. Chen, T.W. Chen, Y.L. Li and R.J. Ramalingam, *Ultrason. Sonochem.*, 57 (2019) 233.
30. S. Palisoc, R.I.M. Vitto and M. Natividad, *Sci. Rep.*, 9 (2019) 18491.
31. J. Zhang, Y. Liu, X. Wang, J. Du, K. Song, B. Li, H. Chang, R. Ouyang, Y. Miao, Y. Sun and Y. Li, *ACS Appl. Mater. Interfaces*, 12 (2020) 57768.
32. X. Sun, Y. Ye, S. He, Z. Wu, J. Yue, H. Sun and X. Cao, *Biosens. Bioelectron.*, 143 (2019) 111607.

33. P.S. Pakchin, M. Fathi, H. Ghanbari, R. Saber and Y. Omidi, *Biosens. Bioelectron.*, 153 (2020) 112029.
34. N. Promphet, P. Rattanarat, R. Rangkupan, O. Chailapakul and N. Rodthongkum, *Sens. Actuators, B*, 207 (2015) 526.
35. L. Wang, L. Hao, W. Qi, X. Huo, L. Xue, Y. Liu, Q. Zhang and J. Lin, *Sens. Actuators, B*, 321 (2020) 128616.
36. J.X. Wang, Y. Zhuo, Y. Zhou, H.J. Wang, R. Yuan and Y.Q. Chai, *ACS Appl. Mater. Interfaces*, 8 (2016) 12968.
37. H. Wang, H. Yu, S. Yin, Y. Li, H. Xue, X. Li, Y. Xu and L. Wang, *Nanoscale*, 10 (2018) 16087.
38. S. Chaiyo, E. Mehmeti, K. Zagar, W. Siangproh, O. Chailapakul and K. Kalcher, *Anal. Chim. Acta*, 918 (2016) 26.
39. Y. Bai, H. Li, J. Xu, Y. Huang, X. Zhang, J. Weng, Z. Li and L. Sun, *Biosens. Bioelectron.*, 166 (2020) 112424.
40. C. Karaman, B.B. Yola, O. Karaman, N. Atar, İ. Polat and M.L. Yola, *Microchim. Acta*, 188 (2021) 425.
41. W. Mao, B. Cai, Z. Ye and J. Huang, *Sens. Actuators, B*, 261 (2018) 385.
42. W. Li, C. Ma, Y. Song, C. Hong, X. Qiao and B. Yin, *Nanotechnology*, 31 (2020) 185605.
43. B.S.R. Kouamé, S. Baranton, P. Brault, C. Canaff, W.C. Coral, A. Caillard, K.D. O. Vigier and C. Coutanceau, *Electrochim. Acta*, 329 (2020) 135161.
44. M. Zhao, J. Shang, H. Qu, R. Gao, H. Li and S. Chen, *Anal. Chim. Acta*, 1095 (2020) 93.
45. W.J. Shen, Y. Zhuo, Y.Q. Chai, Z.H. Yang, J. Han and R. Yuan, *ACS Appl. Mater. Interfaces*, 7 (2015) 4127.
46. L. Zhou, T. Wang, Y. Bai, Y. Li, J. Qiu, W. Yu and S. Zhang, *Biosens. Bioelectron.*, 150 (2020) 111964.