The Application of Biosensors Based on Nanomaterials in Early Disease Diagnosis and Optimization of Intelligent Algorithms

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Abstract. With the continuous development of nanotechnology and intelligent algorithms, there are more and more biosensors based on nanomaterials and those optimized by intelligent algorithms. Both offer significant assistance in various aspects of biosensors used in early medical diagnosis. Nanomaterials often have smaller sizes and better electrical conductivity, which significantly enhance the sensitivity of sensors and the transmission of signals. Intelligent algorithms also offer significant assistance in the structure, simulation, and parameter adjustment of sensors. To better understand the assistance of nanomaterials and intelligent algorithms to biosensors, this paper explores both. This article classifies nanomaterials and intelligent algorithms, and introduces the advantages, disadvantages and functions of different types of nanomaterials and intelligent algorithms with practical examples. It also discusses how to correctly utilize nanomaterials and intelligent algorithms. Overall, this paper reviews the application of biosensors based on nanomaterials in the early diagnosis of diseases and the optimization of intelligent algorithms.

Keywords: Nanomaterials, nano-biosensor, intelligent algorithm, medical diagnosis, dimension.

1. Introduction

With the rapid development of nanotechnology, the application of biosensors based on nanomaterials in the medical field is becoming increasingly widespread.

A biosensor is a device or probe that integrates a biological element, such as an enzyme or antibody, with an electronic component to generate a measurable signal. The electronic component detects, records, and transmits information regarding a physiological change or the presence of various chemical or biological materials in the environment. Biosensors come in different sizes and shapes and can detect and measure even low concentrations of specific pathogens, or toxic chemicals, and pH levels [1]. In the early diagnosis of medical care in modern society, when traditional biosensors are used to detect target substances, problems such as cumbersome detection processes, repetitive and complex steps, high costs, poor durability, and a shortage of technical personnel are encountered. Nanomaterials refer to materials in which at least one dimension of the three-dimensional space is at the nanoscale or composed of them as basic units. They feature high strength, good electrical conductivity, nanoscale size, high stability, and are compatible with biomolecules [2]. Different characteristics provide the possibility of improving the performance of biosensors and increasing the power of detection through size and morphology control. Therefore, biosensors based on nanomaterials are also becoming increasingly popular in early medical diagnosis. The basic working principle of nano-biosensors is along the same lines of conventional macro- and micro-counterparts, but they are constructed using nanoscale components for signal or data transformation. Meanwhile, various intelligent algorithms can also assist in optimizing biosensors. By integrating various intelligent algorithms, multiple structural parameters of sensors can be optimized to overcome the shortcomings of traditional methods and further enhance the performance of sensors in various aspects, such as sensitivity and signal transmission time.

This article will discuss the application of biosensors composed of different nanomaterials in the early diagnosis of diseases and, in combination with various intelligent optimization algorithms, look forward to the future of nanomaterial biosensors.

2. Nanomaterials of Different Dimensions

This article will classify nanomaterials based on their different appearance characteristics: Three-dimensional nanomaterials can accommodate three variables, such as graphite; Two-dimensional nanomaterials can accommodate two variables, such as graphene; One-dimensional nanomaterials can only accommodate one variable, such as carbon nanotubes. Zero-dimensional nanomaterials, such as fullerenes, remain static at isolated points [3].

2.1. Biosensors Based on Zero-Dimensional Nanomaterials

Overall features: All sizes are at the nanoscale, typically including nanodots, nanoparticles (NPs), quantum dots (QDs), etc. They have a high specific surface area and strong surface reactivity.

Precious metal nanomaterials such as gold, silver and palladium have been widely applied in the field of electrochemical sensing due to their good electrical conductivity, fast electron transfer rate and good biocompatibility. Among them, AuNPs are the most widely used and extensively studied precious metal nanomaterials.

Gold nanoparticles have excellent electronic conductivity. Wang et al. utilized this property to construct an AUNPS-composite nanofiber electrochemical sensor for the detection of gastric cancer-related genes, with a recognition rate exceeding 50%. It is precisely the conductivity of AuNP that enhances the stability of chemical signal detection. Gold nanoparticles also have a unique SERS enhancement effect and can amplify fluorescence signals. Qi et al. have established a SERS and fluorescence dual-channel microfluidic platform, achieving telomerase detection at the single-cell level. Li et al. also utilized the fluorescence quenching/enhancement property of AuNP to achieve dynamic intracellular detection. They designed a dual-color fluorescent AuNP probe (nanoflares) that can simultaneously detect miR-21 and miR-141 within living cells, enabling miRNA multiplex imaging and enhancing diagnostic sensitivity [4].

In addition to various metal nanomaterials, zero-dimensional non-metal nanomaterials can also be used to fabricate biosensors. Take Carbon quantum dots (CQDs) as an example. Carbon quantum dots are serendipitously discovered by Xu in 2004. It features excellent electrochemical activity and electronic conductivity, as well as good biocompatibility and stability. Yu et al. utilized its high electrochemical activity to enhance the electron transport rate and amplify the signal. Meanwhile, the rich functional groups (amino and hydroxyl groups) on its surface provided the binding sites for DNA probes and APTES to fabricate CQDs/APTES composite nano memes, which were used as the electrode modification layer. Then a stem-ring structure DNA probe (HSP) was fixed on its surface for the detection of HPV-16 DNA. The detection range of the sensor finally made is relatively large. It has good selectivity and can distinguish non-targets such as mismatched DNA and HPV-18. At the same time, it has good stability, and the signal remains above 84% after being stored for 15 days [5]. This also confirms that CQDs is of great help to the signal transmission of sensors and the stability of sensors.

2.2. Biosensors Based on One-Dimensional Nanomaterials

Overall features: Their length is much greater than their diameter and thickness. Typical examples include nanowires, nanorods, nanotubes, and nanofibers. They often have a high specific surface area and excellent electron and ion transport performance.

Carbon nanotubes (CNTs) are one-dimensional nanomaterials with tubular structures, featuring strong tensile strength, excellent electrical conductivity and large specific surface area. Electrochemical sensors prepared based on CNTs have the characteristics of accelerated electron transfer speed, increased sensitivity to detect target substances, enlarged specific surface area of electrode modification layers and easy miniaturization [6]. Wang et al. utilized the high conductivity of Multi-Walled Carbon Nanotubes (MWCNTs) to accelerate electron transport and enhance the efficiency of electrochemical reactions. Meanwhile, the large specific surface area feature of MWCNTs can provide more sites for enzyme molecule immobilization. Based on this, they fabricated

MWCNTs/ Chitosan (CS)/ Glucose Oxidase (GOx) modified electrodes and constructed electrochemical glucose sensors. Compared with traditional electrodes, the response current of the electrodes of this sensor is significantly increased, and the detection range is wider. At the same time, the sensor also demonstrated excellent repeatability and stability. By taking advantage of these properties of carbon nanotubes, Kumar et al. modified functionalized MWCNTs on the electrode surface and immobilized antibodies against prostate-specific antigen (PSA). The resulting sensor could accurately identify PSA at low concentrations, with a detection limit significantly lower than that of conventional methods, thereby enhancing the sensitivity and specificity of clinical diagnosis of prostate cancer [3].

Nanorods are also a type of one-dimensional nanomaterials. Nanorods are often used as simple electrochemical modifiers providing a highly specific process. They have high specific surface area and excellent electronic transport characteristics brought by one-dimensional structure, which are conducive to directional transport and interface interaction. At the same time, they also have good biocompatibility and can significantly enhance the fixation efficiency and electrochemical response performance of biomolecules. They are usually prepared from gold, graphene, manganese, zinc, or iron oxide, or the combination of these materials. Zhu et al. demonstrated a ZnO NRs-based FET biosensor for continuous glucose monitoring using AC frequency mixing. The fabricated sensor achieved a high sensitivity of 1.6 mA $(\mu M^{-}cm^{-2})^{-1}$with a concentration detection limit of 1 μM, and exhibited an excellent long-term stability on continuous monitoring for 38 h [1].

2.3. Biosensors Based on Two-Dimensional Nanomaterials

Overall features: The thickness is at the nanometer level, and the length and width are much greater than the thickness. Therefore, this type of material has a large surface area and features high electron mobility and active interlayer reactions.

Take graphene as an example. It has a large surface area, good electrical conductivity, and remarkable electrochemical properties, including a large potential window, low charge transfer resistance, high electrochemical activity, and rapid electron transfer. It is an ideal electrode material for detecting biomarkers, cells, DNA, glucose, pH values, and other analytes. In addition, graphene and its oxygen-containing derivatives, including graphene oxide (GO) and REDOX graphene (RGO), are also becoming an important type of nanomaterial in the field of biosensors. The presence of oxygen-containing functional groups makes GO nanosheets highly hydrophilic, which is conducive to chemical functionalization. Therefore, due to the special properties of graphene and its derivatives, there are more and more biosensors based on them [7].

Due to the high electrical conductivity and large specific surface area of graphene, it can fix a large number of DNA probes and accelerate electron transfer. Rasheed & Sandhyarani et al. constructed graphene-DNA-AunPs modified glassy carbon electrodes (GCE), which can effectively detect the breast cancer-related gene BRCA1, thereby facilitating early screening of breast cancer. Salahandish et al. constructed N-doped Graphene/AgNPs/PANI nanocomposite electrodes for the detection of breast cancer-related micrornas (miR-21). It is also very helpful for the early screening of breast cancer [8].

2.4. Biosensors Based on Three-Dimensional Nanomaterials

Overall features: The spatial structure is complex, usually featuring large pore volume, high surface area, and excellent material transport capacity.

For example, Dendrimers are nanometer-scale 3D macromolecules in the size of an average protein-, and are hyper-branched, mono-dispersed, and star-shaped, with a high density of surface functional groups. They have been used extensively in various biosensors, diagnostics, and drug delivery based on electrochemistry, fluorescence, SERC, impedimentary, and SPR. Dendrimer-based biosensors increase analytical sensitivity, stability, and reproducibility but reduce no specific interactions [1]. Maria Soler et al. designed BAPAD dendritic molecules with amoxicillin groups, which formed a uniform and stable recognition layer on the surface of gold nanoplates, achieving

direct serum detection of specific IgE. The detection limit was 0.6 ng/mL, which was approximately twice as sensitive as traditional SPR. And it is highly consistent with the clinical Im-munoCAP results [9].

Moreover, Co-based materials have a tunable geometrical structure to provide a large surface area for the exposure of several accessible active sites towards extending the contact area with dopamine molecules. An urchinlike microsphere structure assembled with a large number of nanoneedles can endow Co-based materials with a high surface area, several accessible catalysis sites, a short path for electron transfer towards accelerating reaction kinetics, and abundant surface space for fast electrolyte/reactant diffusion and penetration, thereby ensuring an expected electrocatalytic activity. Based on these characteristics, Thi Luu Luyen Doan et al developed a high-performance non-enzymatic electrochemical sensor based on urchin-like CoP3/Cu3P heterostructured nanorods supported on a three-dimensional porous copper foam, namely, CoP3/Cu3P NRs/CF, for the detection of dopamine. It exhibits excellent catalytic activity, sensitivity, and selectivity for dopamine detection under simulated human body conditions at a physiological pH of 7.25 (0.1 M PBS) at 36.6ºC [10].

After a comprehensive comparison, biosensors made of different nanomaterials are all different. 0-dimensional nanomaterials often can better exert their optical properties, but due to their size, their ability to amplify signals is limited. One-dimensional nanomaterials have good directionality, and the signal transmission speed of sensors is relatively fast. Two-dimensional nanomaterials have a relatively high electron mobility and can be used for optical and electrical detection, but there is still some room for improvement in the stability of sensors. Sensors made of 3D nanomaterials have relatively comprehensive performance, but they are often costly and difficult to produce on a large scale. Table 1 is a summary table of the properties of different nanomaterials. Therefore, nowadays, biosensors based on nanomaterials often take into account multiple aspects comprehensively, including signal transmission rate, detection sensitivity, manufacturing cost, etc., to create more comprehensive biosensors by integrating various types of nanomaterials.

Table 1. Classification Table of Nanomaterials

Types	Features	Advantages	Disadvantages	Examples
Zero-dimensional nanomaterials	All dimensions are at the nanoscale	Excellent optical performance, easy functionalization and high specific surface area	Easy to gather and some are toxic	AuNPs, QDs
One-dimensional nanomaterials	Only the length is much larger than the nanoscale, while the diameter and thickness are limited to the nanoscale.	High electrical conductivity, strong directionality and high sensitivity	Prone to tangling	CNTs, Nanorods
Two-dimensional nanomaterials	The thickness is limited at the nanoscale, while the length and width are much greater than the thickness.	Extremely large specific surface area, excellent electrical performance and multiple functions	Poor stability	Graphene
Three-dimensional nanomaterials	It extends to the macroscopic scale in all three dimensions, but the material is assembled from 0D/1D/2D units, and the feature size is still at the nanometer level.	High porosity, signal amplification, multi-functional combination	The synthesis is complex, the stability is poor and the cost is high	3D Graphene foam, Dendrimer-Based Biosensors

3. Intelligent Algorithem

Although nanomaterials in various dimensions have comprehensively enhanced the performance of biosensors, there is still much room for improvement, such as complex signals and high noise. The

parameter space is huge; Experiments and simulations take a long time. In this era when various intelligent algorithms are rampant, in response to these deficiencies, different intelligent algorithms can optimize the response of biosensors. The following will discuss several different optimization methods of intelligent algorithms for biosensors.

3.1. Optimization of Sensor Parameters and Structure

Firstly, regarding the parameter optimization and structural design of biosensors, due to the vast parameter space of biosensors, using algorithms for global search and multi-objective optimization can further enhance the performance of the sensors. There are many intelligent algorithms used, such as Genetic Algorithm (GA), Particle Swarm Optimization (PSO), Differential Evolution (DE), and Improved Differential Evolution (IDE). Through these algorithms, the parameters of the material composition of the sensor and the structural shape of the sensor can be comprehensively optimized, enabling the sensor to achieve the most balanced performance among sensitivity, figure of merit (FOM), dynamic range detection (DRD), etc.

SPR sensors are widely used in the biological detection of nucleic acids, cells, proteins, hormones, etc. However, when detecting ultra-low concentrations of target substances such as single molecules, their sensitivity is significantly insufficient. In response to these deficiencies, Tingting Liu et al. proposed a multi-objective optimization framework, with algorithms at the core to enhance the performance of SPR sensors. They incorporated sensitivity (S), quality factor (FOM), and depth quality factor (DFOM = S/FWHM×DRD) into the objective function simultaneously. Search for an algorithm that, through the geometric balance in three-dimensional space, ensures that the three are maximized while minimizing the differences, thereby achieving comprehensive performance optimization. Ultimately, after trying various intelligent algorithms, particle swarm optimization performed best in high-dimensional continuous optimization problems and was finally combined. Multiple optimal solution sets (2214 groups) obtained by PSO were used, and then k-means clustering was employed to screen out the design parameters with the smallest process error and the highest stability: incident Angle 62.5°, chromium film thickness 9.1 nm, and gold film thickness 51.6 nm. The sensitivity S of the optimized sensor has increased by 230.22% to 24,482.86 nm/RIU. FOM increased by 110.94%, and DFOM increased by 90.85%. The detection limit (LOD) was reduced to 54 ag/mL (0.36 aM), successfully achieving detection at the single-molecule level [11].

3.2. Signal Processing and Data Modeling

In addition, intelligent algorithms can also be used for data modeling to further optimize signals. The initially collected signals often contain various noises and multiple complex signals. Through various intelligent optimization algorithms, nonlinear mappings can be established between these complex electrochemical and photoelectric signals and inputs such as the concentration and refractive index of biomolecules, thereby achieving the transformation from "noisy data" to "accurate prediction". Commonly used ones include PLS, BP neural network, RBF network, ANN (MLP), etc.

The MXene/ graphene composite electrochemical sensor is used for blood glucose detection. It adopts Ti_3C_2Tx MXene and graphene composite film as the sensitive electrode material. They have abundant active sites and excellent electrical conductivity, which can effectively catalyze the glucose oxidation reaction and generate stable electrochemical signals. Although sensors can provide highly sensitive signals, the data has problems such as nonlinearity, noise, and variable redundancy. In order to further improve the fitting degree and prediction accuracy between the sensor signal and the actual blood glucose concentration; Minrui Bai et al. adopted the RBF network with better nonlinear fitting ability. Firstly, the data was preprocessed: the points deviating from the normal distribution in the electrochemical signal were eliminated to avoid misleading the model; Remove the interfering variables unrelated to blood glucose and extract the electrochemical features highly correlated with glucose concentration to reduce the data dimension. Subsequently, the input electrochemical signal is mapped to a high-dimensional space, and the nonlinear relationship between the signal and the blood glucose concentration is fitted using the Gaussian basis function. After passing through the

RBF network, the goodness of fit R^2 was increased to 0.9895. The prediction curve for blood glucose almost coincided with the actual blood glucose concentration curve, significantly improving the accuracy and stability of blood glucose detection by the MXene/ graphene sensor [12].

3.3. Accelerated Simulation and Design

Intelligent algorithms can also greatly facilitate the simulation of biosensors. The design and optimization of nano-biosensors usually rely heavily on numerical simulation. Traditional methods such as the finite-difference time-domain method (FDTD) and the finite element method (FEM), although they have high accuracy, involve large computational loads and are very time-consuming. Every time there is a change in parameters, the simulation has to be redone, which greatly limits the efficiency of sensor design. Especially when exploring large-scale parameter Spaces, relying solely on FDTD/FEM is almost impossible.

The nano-plasma biosensor is composed of a silicon-based photovoltaic detector and a top nano-plasma structure. The plasma structure acts as an optical filter, and its transmission spectrum varies with the refractive index of the biological sample. The light is absorbed by the detector and converted into an electrical signal, which contains information about the biological sample. When biological samples with different refractive indices act on the sensor surface, the I-V curve (current-voltage characteristic) changes accordingly, so the sample characteristics can be analyzed through photoelectric response. To find the optimal central wavelength (λ) and half-width (FWHM) of the light source, Samaneh Hamedi et al. utilized an artificial neural network and, after repeated training, obtained the optimal network topology of 3-5-4-4-6-21. Through artificial neural networks, complex physical models can be approximated quickly with a small amount of data, greatly reducing the computational load and modeling time. The optimal working conditions of the sensor are ultimately obtained: when the wavelength is 735 nm and the FWHM is 70 nm, both the sensitivity and responsivity can be optimized simultaneously [13].

4. Conclusion

This article provides an overview of biosensors based on different nanomaterials and their applications in the medical diagnosis period, and also introduces several different types of intelligent optimization algorithms. Through the classification of nano-biosensors, readers can better understand the advantages and disadvantages of different nanomaterials and their application scenarios. Zero-dimensional nanomaterials have good optical properties and a high specific surface area, but they are prone to aggregation. One-dimensional nanomaterials have strong directionality and good electrical conductivity, but they are prone to entanglement. Two-dimensional nanomaterials have excellent electrical properties but relatively poor stability. Three-dimensional nanomaterials can achieve multifunctional composites, but their preparation costs are relatively high. In medical diagnosis, nano-biosensors are confronted with brand-new problems. It is necessary to select appropriate nanomaterials based on different situations to produce more comprehensive nano-biosensors. The preparation of biosensors needs to take into account various demands: multi-functionality, sensitivity, production cost, etc. A single material often cannot meet the multi-faceted requirements of biosensors. Therefore, biosensors composed of multiple different nanomaterials will be more competitive. In addition, this article also discusses intelligent optimization algorithms. Several different types of intelligent algorithms not only facilitate the manufacturing of nano-biosensors but also enhance their performance and comprehensive capabilities. Of course, nano-biosensors and related intelligent optimization algorithms are still in the development stage and still face many problems, such as insufficient sensor stability, the need to improve biocompatibility, and the inability to conduct long-term monitoring within living organisms. In the future, researchers will not only be able to develop nano-biosensors for long-term in vivo monitoring, but also intelligent sensors with adaptive capabilities and intelligent responses. It is believed that with the continuous advancement of nanotechnology, algorithmic technology and other scientific and technological advancements, nano-

biosensors will possess more comprehensive functions and be more widely used in various fields such as medicine.

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