

Applications of Metal-Organic Frameworks, Nanomaterials, and Graphene in Biosensors: From Individual Properties to Synergistic Integration

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Abstract. Biosensors display sensitive, stable and multifunctional sensing performance, but can not be accurately deployed to detect trace markers. Recently, three types of functional materials, metals-organic frameworks (MOFs), nanomaterials, and graphene, have been shown to offer excellent potential in biosensing due to their physicochemical properties. In this review, this paper summarise the main features and typical applications of these three types, and describe their signal transduction and amplification mechanism. It has been reported that each class offers different sensing performance advantages, including flexible multidisciplinary integration by their structure, nanomolecular optical transduction by quantum confinement and plasmonic resonance, and, graphene as a perfect electrode substrate because of its good electron conductivity. The combination of all three materials will overcome shortcomings of single-material systems, offering a theoretical basis for highly sensitive, multifunction and portable biosensing systems. Such advancements hold significant promise for clinical diagnostics and point-of-care testing, where the accurate and reliable detection of trace biomarkers is critical for early disease diagnosis and personalized treatment.

Keywords: metal-organic frameworks, nanomaterials, graphene, biosensors, signal amplification

1. Introduction

The detection performance of biosensors fundamentally depends on the physicochemical properties of the interface materials. Traditional materials have limitations in terms of sensitivity, stability, and multi-function integration, making it difficult to meet the precise detection requirements of trace biomarkers [1, 2]. In recent years, metal-organic frameworks (MOFs), nanomaterials, and graphene, with their unique functional characteristics, have provided new opportunities for the construction of high-performance sensing platforms [3-5].

Recent studies have shown that MOFs, with their extremely high specific surface area and tunable pore sizes, have significant advantages in enzyme protection and signal amplification [6, 7]; nanomaterials achieve high-sensitivity optical conversion through quantum confinement and plasmon resonance effects [8]; graphene, with its excellent electron conductivity and two-

dimensional planar configuration, becomes an ideal electrode modification substrate [1, 2]. However, a single material system is difficult to balance multiple properties, and how to achieve the synergistic advantages of these three types of materials remains the current research focus.

This article systematically reviews the core characteristics and typical applications of three types of materials, deeply analyzes their signal conversion mechanisms and performance advantages, and then proposes a collaborative integrated sensor design concept. The aim is to provide a theoretical basis for the development of high-sensitivity, multi-functional, and portable biological sensing platforms, and to promote their practical applications in real-time detection and health management [9, 10].

2. Metal-organic frameworks and related materials

2.1. Core material characteristics of MOFs

MOFs are crystalline porous materials formed by the self-assembly of inorganic metal nodes (such as Zn^{2+} , Cu^{2+} , Fe^{3+} , Zr^{4+} and lanthanide ions) and multi-rotating organic ligands through coordination bonds. Their extremely high specific surface area and regular, tunable pore diameters make them excellent host matrices. Through physical embedding or in-situ growth strategies, they can efficiently load biological enzymes, signaling molecules or nanomaterials, and provide nanoscale reaction channels for substrate diffusion and product transport [6, 7]. On the other hand, by selecting specific metal centers or performing post-synthesis modifications on the materials, MOFs themselves can act as signal transduction elements, and further expand their covalent coupling capabilities with biological recognition probes [7]. This characteristic of integrating carrier functions, catalytic functions and signal output functions, combined with their clear crystal structure and controllable chemical environment, provides a "programmable" molecular platform for constructing complex sensing interfaces and achieving multi-component synergy [6, 7].

2.2. Sweat multi-marker monitoring sensor based on MOF-74/enzyme/argdot biomimetic mineralization

The core of the sweat multi-index monitoring sensor strategy based on MOF-74/enzyme/Argdot biomimetic mineralization lies in using MOF-74 as the biomimetic mineralization platform and co-packaging the recognition elements with the signal enhancement elements. The porous structure of MOF-74 protects the enzymes from being inactivated by the external environment while allowing substrate molecules to freely enter the pores for enzymatic reactions [6].

The experimental results confirmed that the enzyme electrode, after being encapsulated with MOF-74, could maintain over 94% of its initial current response even after 60 days of storage at 4°C. This is attributed to the anchoring and protective effect of the rigid MOF framework on the enzyme conformation, effectively overcoming the inherent defects of free enzymes, such as susceptibility to denaturation and inactivation [6].

Based on the nanocomposite interface formed between Argdot and Prussian blue, this strategy exhibits excellent electrocatalytic activity toward the enzymatic reaction product H_2O_2 . Compared to free enzymes or simple MOF/enzyme sensors, its detection sensitivity for glucose, lactate, and xanthine improved by approximately 35% to 59%, fully demonstrating the integrated advantages of MOFs as multifunctional carriers in achieving "protection-catalysis-conduction" integration [6]. Additionally, the sensor's robust anti-interference capability and wide linear range that fully covers physiological concentration intervals successfully validated its feasibility for dynamic monitoring in

real human activities, highlighting the great potential of MOF-based sensors in the field of non-invasive instant diagnostics [6].

2.3. Ultra-sensitive MicroRNA detection platform based on mof energy transfer effects

The microRNA ultrasensitive detection platform based on MOF energy transfer effects fully utilizes the optical and electrochemical properties of MOFs. On one hand, certain MOFs (such as those containing Cu^{2+} or Fe^{3+}) can serve as highly efficient fluorescence quenchers, suppressing the fluorescence of dye-labeled single-stranded DNA probes adsorbed on their surfaces via photo-induced electron transfer (PET) or fluorescence resonance energy transfer (FRET) mechanisms [7]. On the other hand, by introducing luminescent ligands or lanthanide metals, MOFs can function as excellent electrochemiluminescence (ECL) or fluorescence energy donors [6, 7].

This strategy realizes the ultra-high sensitivity detection of miRNA, and its detection limit can be as low as am level, which is due to the fact that MOF can provide extremely low background signal when it is used as a quenching agent, and its efficient luminous efficiency and loading capacity can produce strong reporting signal when it is used as an energy donor. When the target miRNA induces the probe to release or pull close from the MOF surface, it forms a significant signal "switch" change, thus greatly improving the signal-to-noise ratio [7]. The detection system adopts a homogeneous mode based on fluorescence quenching. Due to the high-efficiency adsorption and quenching ability of MOF nano probe for nucleic acid probe, there is no need for complex electrode modification and cleaning steps, and the operation is simple and the response is fast [7]. In addition, by combining the polychromatic probes labeled with different dyes with MOF, the non-specific adsorption of single stranded DNA and the broad-spectrum quenching or energy transfer effect of different dyes can realize the synchronous analysis of a variety of miRNAs, showing the high-throughput detection potential as an ideal multi-channel optical sensing platform [7].

3. Nanomaterials

3.1. Core material characteristics of nanomaterials

Nanoscale materials are material systems in the range of 1 to 100 nanometers on at least one-dimensional scale. When the size of the material is reduced to the nanometer level, the quantum size effect, surface effect and macroscopic quantum tunneling effect will cause fundamental changes in its physical and chemical properties, making it present different optical, electrical and magnetic properties from the macroscopic bulk materials, and become an ideal energy conversion material for the construction of high-sensitivity biosensors [4, 8].

In terms of optical properties, when the size of the semiconductor material is equivalent to its exciton Bohr radius, its electronic energy levels are split from the continuous state to the discrete state, resulting in the quantum confinement effect, which makes the quantum dots exhibit adjustable size fluorescent emission, wide absorption spectrum, narrow emission spectrum and excellent optical stability, which is suitable for simultaneous detection of multiple targets and long-term dynamic monitoring [8]. Upconversion nanoparticles achieve anti Stokes luminescence by doping lanthanide ions, which can convert low-energy near-infrared light into high-energy visible or ultraviolet light, so as to eliminate the interference of spontaneous fluorescence of biological samples and improve the detection signal-to-noise ratio [8].

In terms of electromagnetic properties, noble metal nanoparticles can produce local surface plasmon resonance effect under the action of incident light, resulting in strong absorption and

scattering of light at specific wavelengths, and the formation of enhanced local electromagnetic fields around them [2, 8]. This effect can not only realize label free detection through the shift of absorption peak, but also be used for surface enhanced Raman scattering and metal enhanced fluorescence, so that the detection sensitivity can be improved by an order of magnitude [4].

In terms of interface properties, the high specific surface area volume ratio of nanomaterials provides sufficient active sites for the immobilization of biometric elements, which significantly improves the probe load density and recognition efficiency. Gold nanoparticles can conveniently modify thiolated biomolecules through gold sulfur bonds to build a stable sensing interface [8]. Magnetic nanoparticles can achieve rapid separation and enrichment of target molecules under the action of magnetic field, effectively simplifying the sample pretreatment process [9].

In terms of catalytic performance, some nano materials themselves have the ability to simulate the catalytic activity of natural enzymes, and can be used as nano enzymes to catalyze the transfer of electrons between the object to be measured and the electrode surface [4, 10]. Metal nanoparticles, their oxides and sulfides exhibit excellent catalytic performance in electrochemical biosensors, which can realize direct electrochemical detection of enzymatic reaction products, avoiding the use of unstable and expensive natural enzymes [10].

3.2. Nanomaterial-based nucleic acid detection for pathogens

Although the traditional pathogen nucleic acid detection method has high sensitivity, it relies on complex thermal cycle instruments and professional operators, which limits its application in the environment with limited resources [8]. The nucleic acid detection platform based on nano materials uses its unique optical properties to build a homogeneous, fast and ultra sensitive detection system, avoiding the dependence on thermal cycle and complex washing steps [8].

The nucleic acid detection platform based on luminescent resonance energy transfer uses UCNPs as energy donor and AuNPs as energy receptor to modify complementary nucleic acid probes respectively. When the target H7 gene exists, the UCNPs target AuNPs sandwich structure is formed through nucleic acid hybridization, which shortens the distance between the donor and the receptor to the effective range of LRET, resulting in the quenching of UCNPs luminescence by AuNPs [8]. The detection limit of this method for H7 subtype gene can reach 7 pM, and it can specifically recognize the target sequence in the mixed system, and has no obvious response to other subtypes, which fully reflects the high sensitivity and selectivity of LRET technology [8].

The near-infrared excitation characteristics of UCNPs in this platform fundamentally eliminate the spontaneous fluorescence interference of biological samples, make the detection background close to zero level, and significantly improve the signal-to-noise ratio [8]. At the same time, the homogeneous detection mode based on LRET does not require electrode modification and repeated washing, which greatly shortens the detection time and is suitable for rapid response to sudden infectious diseases [8]. In addition, by replacing the nucleic acid probe sequence, the platform can be easily applied to the nucleic acid detection of other pathogens, showing good versatility [8].

3.3. Nanomaterial-based colorimetric rapid detection test strips

The core innovation of the rapid test strip based on color change lies in utilizing the LSPR properties of AuNPs to directly convert the molecular recognition event into a visible color signal, enabling immediate detection of the target and simplifying the complex detection process into an operation mode similar to that of a pregnancy test strip [8].

The colorimetric detection method based on antisense oligonucleotide modification of AuNPs is used for the detection of the N gene of SARS-CoV-2. Two segments of ASO sequences are designed to be complementary to different regions of the N gene, and are modified on the surfaces of two groups of AuNPs. When the target is present, the two segments of ASO simultaneously hybridize with the target, forming a cross-linked network structure that induces the aggregation of AuNPs [8]. This method can complete the detection within 10 minutes, and the results can be directly judged visually: when the target is present, the solution is blue-purple, and when there is no target, it remains wine red [8]. The detection sensitivity can reach ng level, and it has high specificity for SARS-CoV-2 [8].

This system fully utilizes the LSPR effect of AuNPs, and its strong absorption and scattering signals give the colorimetric method extremely high colorimetric efficiency [2, 8]. By regulating the plasmon coupling between nanoparticles, the signal is effectively amplified, converting the molecular recognition event into a readily observable physical signal [8]. The test strip platform based on AuNPs adopts an integrated paper-based chip design, eliminating the cumbersome separation and washing steps. It is simple to operate, does not require professional training, and has controllable material costs, making it suitable for large-scale production and promotion [8]. This diversified signal conversion mechanism enables nanomaterials to meet a wide range of needs, from precise quantitative laboratory analysis to rapid on-site screening, and shows broad application prospects in resource-limited areas [8].

4. Graphene and its derivatives

4.1. Core material characteristics of graphene

Graphene is a two-dimensional honeycomb lattice structure formed by carbon atoms arranged in sp^2 hybrid orbitals. Its derivatives mainly include graphene oxide and reduced graphene oxide [1, 2]. These carbon-based two-dimensional materials exhibit outstanding performance in the field of biosensing due to their unique electronic band structure and planar configuration [1].

The sp^2 hybridized carbon atoms in graphene form a highly delocalized large π conjugated system, giving it extremely high carrier mobility, making it an ideal electrode modification material. It can effectively accelerate the electron transfer rate between the electrode and biological molecules, significantly enhancing the response signal strength and response speed of electrochemical sensors [2]. Graphene has an extremely high theoretical specific surface area, much higher than that of carbon nanotubes and graphite, enabling it to serve as an excellent carrier platform. Through π - π stacking, electrostatic adsorption or covalent bonding, it can efficiently load a large number of biological recognition elements, thereby significantly improving the capture efficiency and detection sensitivity of the sensor [1, 2].

Graphene oxide, as an important derivative of graphene, has abundant oxygen-containing functional groups on its basal plane and edges, which endows the material with excellent water dispersibility and biocompatibility, and can serve as a covalent coupling active site for the stable fixation of biological molecules [1, 5]. Through chemical, thermal or electrochemical reduction methods, the oxygen-containing functional groups can be partially removed to obtain reduced graphene oxide. While restoring its conductivity, it retains some defects and functional groups, providing an effective means to regulate the conductivity and surface chemical properties of the material [2]. In addition, graphene oxide has efficient energy transfer and electron transfer quenching capabilities for organic fluorescent dyes. It can quench the fluorescence of dye-labeled probes adsorbed on its surface through fluorescence resonance energy transfer or photo-induced

electron transfer mechanisms. This property makes it an ideal platform for constructing "turn-on" type homogeneous optical biosensors [1].

4.2. Graphene-based electrochemical biosensors for rapid and highly sensitive microorganism detection

Traditional microbial detection methods have limitations such as long time consumption, complex operation or reliance on expensive instruments [1]. Graphene-based electrochemical biosensors utilize their high conductivity and large specific surface area to construct a high-density biological recognition interface, directly converting microbial recognition events into electrochemical signals, achieving rapid and highly sensitive detection [1, 2].

An electrochemical aptamer sensor based on reduced graphene oxide titanium dioxide nanocomposites was developed for the detection of *Salmonella typhimurium*. In this study, the high conductivity of RGO was combined with the good biocompatibility of TiO_2 nanoparticles to construct a synergistically enhanced sensing interface. RGO provides a fast electron transfer channel, and TiO_2 nanoparticles increase the specific surface area of the electrode and provide rich active sites for aptamer fixation [1]. The linear detection range of the sensor for *Salmonella typhimurium* is 10 to 10^8 CFU/ml, the detection limit is as low as 10 CFU/ml, and the detection time is shortened to several minutes [1].

The sensor fully embodies the core advantages of graphene. The high carrier mobility of graphene makes it an ideal electrode modification material, which can effectively accelerate electron transfer and significantly improve the response signal strength and speed [2]. Graphene with a theoretical specific surface area of $2630 \text{ m}^2/\text{g}$ can be used as an excellent carrier platform to efficiently load biometric components. In the detection of *Salmonella*, the large specific surface area of RGO TiO_2 composite provides sufficient active sites for aptamer fixation to achieve efficient capture of target bacteria [1]. In addition, graphene and other nano materials can form a synergistic enhancement effect. The high conductivity of RGO and the large specific surface area of TiO_2 realize the double amplification of the signal [1, 2].

4.3. Graphene-based biosensors for disease biomarker detection

The precise detection of disease markers is of great significance for early diagnosis and treatment [5, 10]. Graphene-based electrochemical biosensors utilize their high conductivity and electrocatalytic activity to directly conduct electrochemical detection of disease markers or achieve highly sensitive detection of tumor cells through sandwich immunological structures [5, 10].

The dopamine electrochemical biosensor based on gold-doped lanthanum oxide nanocomposite combines rare earth metal oxides with gold nanoparticles and fixes tyrosinase, constructing a sensing interface with excellent electrochemical performance [5]. The La_2O_3 nanomaterial provides good electrocatalytic activity and high specific surface area, and the introduction of gold nanoparticles generates a synergistic enhancement effect, further improving conductivity and electron transfer rate [5]. The sensor has a linear detection range of 2 to $100 \text{ }\mu\text{M}$ for dopamine, with a sensitivity of $2.48 \times 10^{-7} \text{ A}/\mu\text{M}$, a detection limit as low as $0.258 \text{ }\mu\text{M}$, and a response time of 30 seconds. The Michaelis constant is $5.649 \text{ }\mu\text{M}$, indicating that the immobilized tyrosinase has a high affinity for the substrate [5].

The sensor shows the multiple advantages of graphene and its derivatives. Graphene can be used as electrode modification material to accelerate electron transfer due to its excellent electron conduction ability. The introduction of gold nanoparticles further enhances the conductivity,

reflecting the potential of graphene based composites in improving the efficiency of signal transduction [2, 5]. The good biocompatibility of graphene provides a suitable microenvironment for the immobilization of biometric elements. In this case, La_2O_3 nanomaterials maintain the biological activity of enzymes [5]. The multifunctional integration capability of graphene is shown by the combination of rare earth metal oxides and gold nanoparticles. The high electrocatalytic activity of La_2O_3 combined with the high conductivity of AuNPs significantly improves the sensitivity and response speed of the sensor [5].

5. Design concept

Graphene or reduced graphene oxide may be used as an electrode substrate because of its high electrical conductivity and large specific surface area to transfer and lock biorecognition atoms. On the substrate, metal-organic (MOF) materials may be introduced to perform their porous structure on high-capacity encapsulation of enzymes while keeping their activity under control, the catalytic activity or optical properties of MOFs can be used for signal amplification, and specific antibodies/nucleic acid aptamers might be wrapped on the surface of the composite material as recognition probes and potentially be used in ultra-sensitive real time dynamic monitoring of disease biomarkers of sweat or serum.

6. Conclusion

This paper reviews the key features and typical applications of three functional materials, namely metal-organic frameworks, nanomaterials and graphene in biosensors design. Metal-organic models, their ultra-high specific surface area, tunable pores and multi-path coupling, provide their advantages for enzyme protection, signal amplification, and multi target detection. Nanomaterial, with their effect of quantum confinement and surface plasmon resonance, provide very sensitive transduction and diversified optical signal output. Graphene, which is extremely high electron conductivity, very large specific surface space, and highly versatile surface chemistry, acts as a natural substrate to build electrochemical sensing interfaces. Typical applications of these three materials thoroughly demonstrate their useful performances in improved sensor sensitivity, stability, response and detection rates.

It has been shown that although each single-material system has its own advantages, any single material cannot simultaneously satisfy the requirements of high sensitivity, good stability and multi-target detection. By combining these three classes of materials, complementary functions and enhanced performance could be possible, which will open new avenues to develop next-generation highly sensitive, multi-functional and portable biosensors. Future research will focus on controlling the construction of multiple-material composite interfaces, jointly optimizing signal transduction, and testing performance in real-world applications such as clinical point-of-care testing and wearable health monitoring, thereby driving the development of biosensor technology with improved precision, integration and intelligence.

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