Recent Advances in Metal-Organic Frameworks for Biomacromolecule Sensing

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Abstract: Metal-organic frameworks (MOFs) are emerging class of ordered porous materials consisting of metal clusters and organic ligands. High porosity, adjustable topology, composition and structural diversity have earned MOFs extensive popularity in various fields, including biosensing. This review focuses on understanding the role of MOFs in biosensing, mainly as efficient signal probes, nanzymes and nanocarriers. It also provides the recent advances of MOFs in sensing biomacromolecules such as protein, peptide, DNA, RNA and polysaccharide. In addition, the challenge, and perspectives, of MOFs in biosensing are presented, based on our opinion.

Keywords: porous materials; metal-organic frameworks; biomacromolecule; biosensing

1. Introduction

Biomacromolecules refer to proteins, nucleic acids, polysaccharides, and others, which exist in and are important components of living organisms. An abnormal biomacromolecule content in organisms usually predicts the occurrence of disease. Therefore, biomacromolecules are widely used as disease markers. Disease-related biomacromolecules can objectively assess normal biological and pathogenic processes, and pharmacological responses to interventions and have been widely used in the identification, classification, early diagnosis and prevention of diseases [1,2]. The quantitative detection of biomacromolecules in biological media has significant clinical value for early physiological dysfunction and tracking disease progression [3]. Therefore, the detection of biomacromolecules with high sensitivity, accuracy, and selectivity plays a positive role in the rapid development of biomedicine.

Metal-organic frameworks (MOFs) are an emerging class of ordered porous materials consisting of metal clusters and organic ligands. As early as 1995, Yaghi et al. reported a novel two-dimensional coordination compound named MOF, which began to receive extensive attention in various fields [4]. However, the application of MOFs was limited by the pore size and stability at that time. In 1999, Yaghi et al. synthesized MOF-5 with a three-dimensional (3D) open framework, which created a new direction for the development of MOFs [5]. The different coordination between metal clusters and organic ligands gives the MOF a variety of topologies. The topological structure of MOFs is determined by the assembly form of secondary building units (SBUs). Based on the SBUs, MOFs can be divided into: MOFs with triangular and square SBUs; MOFs with triangular and square SBUs and hexatopic linker; MOFs with square and tetrahedral SBUs; MOFs with square and trigonal prismatic SBUs; MOFs with square and octahedral SBUs; MOFs with tetrahedral and trigonal prismatic SBUs; and MOFs with square pyramidal and octahedral SBUs [6]. MOFs can be also classified as isoreticular MOFs (IRMOFs); a zeolitic imidazolate framework (ZIF); coordination pillared-layer (CPL); Materials of Institute Lavoisier (MIL); porous coordination network (PCN); and University of Oslo (UiO) series, according to their naming method. All MOF series pos-
To their fine-tunable metal clusters and organic ligands, easily functionalized surface engineering, and unique pore confinement effects, MOFs have broad application prospects in biosensing. Liu et al. summarized the unique characteristics of MOFs in biomolecular sensing and discussed the relationship between the characteristics of MOFs and the detection performance [19]. The synergistic effect of unsaturated metal active sites and pore confinement, endows MOFs with excellent catalytic activity, thus, MOFs are often used for biomacromolecule sensing as nanoenzymes, contributing to the improved sensitivity of methods [20–22]. Additionally, it is possible to design metal clusters or organic ligands that enable MOFs to be used as signal probes or nanocarriers for biomacromolecule sensing [23–26], and some critical reviews have summarized the diverse performance of MOF-based electrochemical and optical biosensors [27,28]. This review summarizes the recent advances in biomacromolecule sensing using MOFs. MOF-based sensing is outlined according to the central role that MOFs play in biosensing, for example, signal probes, nanoenzymes and nanocarriers, and detection substances, such as proteins, peptides, DNA, RNA and polysaccharides. Finally, the challenges and perspectives of MOFs in biosensing are highlighted, based on our opinion.

2. Design and Fabrication of MOFs for Biomacromolecule Sensing

The different binding modes of metal nodes and organic linkers facilitates the fabrication of MOFs with diverse structure, offering great potential for different applications [29,30]. Owing to their diverse compositions and structures, MOFs exhibit excellent optical, catalytic and electrochemical performances. They are also structurally designable and can be easily used to load large amounts of signal probes, enzymes, specific recognition elements and tags. Therefore, MOFs are widely used as signal probes, nanoenzymes and nanocarriers for various biosensing applications.

2.1. MOFs-Based Nano-Probes

2.1.1. MOF-Based Nanoprobes for Optical Sensing

The diversity and combination flexibility between organic and inorganic components in MOFs, as well as the pores, provide sufficient possibilities to regulate the luminescence performance of MOFs. Therefore, MOFs have attracted considerable attention as nanoprobes in the fluorescence and electrochemiluminescence (ECL) fields.

The ideal fluorescent probe for biosensing applications should have suitable excitation and emission wavelengths, a strong response to specific target recognition, good cell permeability, and high biocompatibility and photostability [31]. By introducing lanthanide ions or luminescent organic ligands, luminescent MOFs (LMOFs) can be employed as fluorescent materials for the detection of hormones, disease markers and biological imaging. Table 1 summarized the reported linkers for the synthesis of LMOFs along with the formed MOFs. Lanthanide MOFs (Ln-MOFs) have unique luminescence characteristics, including large Stokes shifts, high specific areas, long decay lifetimes, and well-defined pores. The specific design and preparation of Ln-MOFs can directly affect their luminescence performance. According to the interaction between lanthanide ions and the ligands of MOFs, the strategies for Ln-MOFs preparation mainly includes in-situ composition, ion doping, ion exchange, covalent post-synthetic modification, and coordinated post-synthetic modification [32]. Mondal et al. prepared a white light emitting MOFs by doping Eu3+ and Tb3+ into the micropores of Imidazolate Framework Postdam-1 [33]. Based on the coordination between lanthanide ions and MOFs ligands, Abdelhameed et al. prepared a liminescent nanothermometer by coordinated post-synthetic modification of MIL-68 [34]. Ln-MOFs are widely used in optical sensing applications based on the dynamic quenching effect (DQE), internal filter effect (IFE),
photoinduced electron transfer (PET), and fluorescence resonance energy transfer (FRET) [35]. Qu et al. selected Tb$^{3+}$ and iso-phthalic acid as precursors to prepare fluorescent Tb-MOFs by hydrothermal method [36]. The Tb-MOFs exhibited excellent long-term stability in water and can maintain a high level of emission at high ionic strength and wide pH range. Moreover, dispersed AuNPs can effectively quench the fluorescence of Tb-MOFs. Based on this, a fluorescence sensor based on the IFE, DQE and FRET quenching mechanisms to regulate the fluorescence of Tb-MOFs was reported. Song et al. prepared LMOF by doping Tb$^{3+}$ in situ into bismuth-based MOFs (Tb$^{3+}$-NOTT-220) [37]. The presence of target (5-hydroxytryptamine, HT) can inhibit the energy transfer between Tb$^{3+}$ and ligands, which increased the fluorescence intensity of the ligand and reduce the emission of Tb$^{3+}$. Thus, a ratiometric fluorescence sensor based on Tb-doped MOFs was proposed, and HT was measured based on the DQE, as depicted in Figure 1.

**Figure 1.** (a) HOMO-LUMO energy levels of the sensor and analyte HT (HOMO: highest occupied molecular orbital; LUMO: lowest unoccupied molecular orbital); (b) luminescence response mechanism of the sensor for HT. Reprinted from Ref. [37] with permission by Elsevier.

**Table 1.** The schematic representation of linkers used for the fabrication of LMOFs and the obtained LMOFs.

| Linkers | Metal Ions | LMOF | Ref. |
|---------|------------|------|------|
| ![Diagram](image1.png) | Zn$^{2+}$ | Zn-TCPP | [38] |
| ![Diagram](image2.png) | Zn$^{2+}$ | Zn(TPyTPP)$_{3.5}$(BDC)$_3$ | [39] |
| ![Diagram](image3.png) | Zr$^{4+}$ | BUT-88 | [40] |
Selecting suitable organic ligands is another method to prepare LMOFs. The luminescent ligands used to construct the MOF form a network in the MOF through a 3D connection, which facilitates rapid excited-state energy transfer migration among the luminescent ligands. The MOF framework isolates the luminophore from the solvent molecules, resulting in the high-energy emission efficiency of the luminophore. Tetraphenylpyrazine (TPP) and its derivatives are a new type of heterocyclic aggregation-induced emission light source that has the advantages of good stability, adjustable luminescence color, simple synthesis method, and convenient structure modification [46]. By incorporating TPP units as luminescent ligands into MOFs, TPP-based MOFs can effectively enhance the emission generated by ligand intramolecular rotation restriction in the framework through strong coordination bonds [38]. Ying et al. constructed a fluorescence sensor with TPP-based MOFs as nanoprobe based on DQE. The TPP-based LMOF used Zn$^{2+}$ as metal nodes, tetrakis(4-(pyridin-4-yl)-phenyl)pyrazine (TpyTPP) as neutral ligands, and H2BDC (BDC) as co-ligands, and the resulting LMOF was named [Zn$_3$(TpyTPP)$_{10.5}$(BDC)$_4$]·8DMF [39]. Figure 2 shows the structure of this LMOF.
Carbazoyl dicyanobenzene derivatives are thermally activated, delayed fluorescence emitters with unique luminescence properties [47]. Their emission can be easily modulated by changing the number and position of the carbazole groups or by introducing substituents. Kong et al. designed a fluorescent octagarnyxoxicylic acid ligand with 2,3,5,6-tetraakis(3,6-bis(4-carboxyphenyl)-9H-carbazole-9-yl)tereophthalate and prepared a green light-emitting MOF-based nanoprobe for imaging dual tumor markers in living cells, as depicted in Figure 3 [40]. Porphyrins and their derivatives can also be used as ligands for the preparation of LMOFs, owing to their unique molecular electronics and structures. Sun et al. reported a MOF (MOF-525) with self-fluorescence by connecting porphyrin with a ZrO$_4$(OH)$_4$ cuboctahedral. MOF-525 exhibited a stable red fluorescence emission under excitation [41]. Additionally, Liu et al. reported another zirconium-porphyrin MOF (PCN-222) with a stable fluorescence emission at 675 nm [42]. The Zr-O-P bond between Zr$^+$ and aptamer makes PCN-222 exhibit strong adsorption performance to the dye-labeled aptamer, and the rapid quenching efficiency between H$_2$TCPP ligand and the dye gives the biosensor rapid and ultrasensitive detection performance. In summary, the selection of organic ligands with different properties can endow MOFs with diverse fluorescence emission properties.
Figure 3. Application of green-emitting MOF-based nanoprobes in live-cell dual tumor marker imaging. Reprinted from Ref. [40] with permission by American Chemical Society.

MOFs with both electrochemical activity and optical properties have facilitated the development of ECL. Recently, MOFs have been used to stably immobilize ECL luminophores to increase their ECL response and improve the sensitivity of ECL sensors [48, 49]. The advantages of preparing MOFs with ECL luminophores as ligands are the following: (1) the bridging ligands are immobilized in the MOFs, which suppresses the non-radiative decay caused by intramolecular rotation, vibration, and torsion, thus, the strength and efficiency of ECL can be significantly improved [43]; (2) because ECL luminophores are directly used as ligands, the immobilized content of the ECL luminophores is significantly increased [44, 45]; (3) MOFs can also be modified on the electrode surface as microreactors for ECL reactions, and the diffusion distances of ions, electrons, co-reactants, and co-reactant intermediates can be shortened [50]; and (4) because of the porous matrix of MOFs, both the inner and outer ECL luminophores can be electrically activated and interact with the co-reactants, which effectively improves the utilization of the luminophore [51].

Recently, Wang et al. proposed a self-enhanced ECL emitter, where a dual ligand MOF was synthesized by integrating 9,10-di(p-carboxyphenyl)anthracene (DPA) and N, N-diethylethylenediamine (DEAEA) ligands into a Zn²⁺ metal node, denoted as Zn-DPA/DEAEA (d-MOF). DPA is a typical ECL luminophore and DEAEA is an effective co-reactant. By linking the luminophore and co-reactant in the MOF, d-MOF exhibited an efficient intramolecular electron transfer process. d-MOF exhibited a powerful and ultra-stable ECL performance without any additional co-reactants, as compared to DPA or Zn-DPA mono-ligand MOF [52].

Additionally, ECL luminophores can also be coated in/on MOFs to prepare ECL signal probes, which not only prevents the agglomeration of luminophores but also improves their ECL efficiency. For example, an ECL signal probe with IRMOF-3-enriched CdTe (CdTe@IRMOF-3@CdTe) was reported. The organic ligands (2-amino terephthalic acid) of IRMOF-3 functions as a co-reactant accelerator, so that IRMOF-3 integrates co-reactant accelerators and luminophores to enhance the ECL intensity and stability, as depicted in Figure 4a [53]. It is well known that tris(2,2′-bipyridyl)ruthenium(II) (Ru(bpy)₃²⁺) derivatives exhibit excellent ECL luminescence and electrochemical performance. Mesoporous MOF have been reported to immobilize Ru(bpy)₃²⁺ by the coordina-
tion of metal clusters and COO\(^-\), as depicted in Figure 4b, and a stable and sensitive ECL sensor was developed using luminescence-functionalized MOFs as probes [54].

![Figure 4](image_url)

**Figure 4.** (a) The luminous mechanism of CdTe@IRMOF-3@CdTe ECL probe. Reprinted from Ref. [53] with permission by American Chemical Society. (b) Structure of PCN-777 (A); Scheme of incorporating Ru(bpy)\(_2\)(mcpbpy)\(^{2+}\) inside the Channels of PCN-777 (B). Reprinted from Ref. [54] with permission by American Chemical Society.

### 2.1.2. MOF-Based Nanoprobes for Electrochemical Sensing

Electrochemical sensing is a simple, economical and convenient detection method that uses current as the output signal. The electrode is an indispensable component of electrochemical sensing, and its conductivity directly affects the analytical performance of the method. Furthermore, there is a strong desire to develop electrodes with a surface that exhibits strong affinity towards the target analyte and shows good electrical conductivity. Consequently, the selection of suitable electrode modification materials is key to improving the electrode conductivity. Functional nanomaterials, such as porous MOFs, have received extensive attention as efficient and selective biosensing electrode materials. Ag(I) exhibits excellent electrical conductivity and electrochemical stability. A silver-based MOF (Ag-MOF) was developed as a signal probe for constructing an electrochemical immunosensor. The introduction of the Ag-MOF simplified the operation and stabilized the electrochemical signal [55]. MOFs are also excellent carriers for noble metal nanoparticles (NPs) such as AgNPs, AuNPs, Pt NPs and others, which not only improves the conductivity and electron transfer activity of the NPs, but also prevents the aggregation of NPs to obtain good dispersion for stable signals [56–58].

Some emerging bimetallic MOFs have better electroanalytical capabilities than traditional MOFs and have been gradually applied in the field of electrochemistry. Hu and Li demonstrated that bimetallic MOFs exhibit superior electrochemical activity than monometallic MOFs due to the synergistic effect between the diverse metal centers and the electrochemically active ligand [59,60]. Guo et al. reported a CuNi metal-organic framework (CuNi\(_{x}\)-(HHTP)\(_2\)) for electrochemical aptamer sensing between C6 glioma cells and epidermal growth factor receptor (EGFR), as depicted in Figure 5 [61]. Different from the conventional MOFs, CuNi\(_{x}\)-(HHTP): was composed of long-range delocalized electrons, graphene mimics nanostructures, multiple metallic states, and sufficient oxygen vacancies. With these capabilities, CuNi\(_{x}\)-(HHTP): anchored a large number of aptamers through coordination among metal centers and oligonucleotides, π-π superposition, and van der Waals forces. Thus, the proposed sensor showed low limit of detection of 21 cells mL\(^{-1}\) and 0.72 fg mL\(^{-1}\) for C6 glioma cells and EGFR, respectively.

Ma et al. prepared a Co/Zn bimetallic MOF for electrochemical sensing of dopamine [62]. The doping metal ions improved the chemical environment of stomata, increased the types and spatial arrangement of MOF active sites, and facilitated the electron trans-
fer and exchange with dopamine. The Co\(^{2+}\) and Zn\(^{2+}\) active centers had a synergistic promotion effect, thus the catalytic activity of MOF was significantly increased, and the detection limit of the method was as low as 1.67 nmol L\(^{-1}\). Jalal et al. proposed a Ni-Co-BTC MOF as active materials for electrochemical sensing of doxorubicin, and the bimetallic MOF was successfully applied to determine doxorubicin in the real samples of human urine and serum [63]. Kachouei et al. employed a CoZn MOF for designing a non-enzymatic glucose sensing platform [64]. The synergistic interaction between the polyphase metal centers makes the bimetallic MOF exhibited good electrical conductivity and fast electrochemical reaction. Therefore, the bimetallic MOF-modified electrode possessed excellent electrocatalytic performance for the electrooxidation of glucose.

Figure 5. Schematic diagram of: (A) the preparation of the Cu\(_x\)Ni\(_{3-x}\)(HHTP)\(_2\) MOF; and (B) fabrication of the electrochemical aptasensor based on the Cu\(_x\)Ni\(_{3-x}\)(HHTP)\(_2\) MOF. Reprinted from Ref. [61] with permission by Royal Society of Chemistry.

2.1.3. MOF-Based Nanoprobes for Photoelectrochemical (PEC) Sensing

PEC sensing is a type of detection method with photocurrent as the output signal, and it exhibits a lower background and higher sensitivity than traditional electrochemistry. The PEC activity (conductivity and photoresponsiveness) and the stability of the electrode materials affect the photoelectric conversion efficiency of the sensor. Owing to the excellent physicochemical properties of MOFs, significant efforts have been made to design MOF-based PEC materials with excellent photon-electron conversion efficiency and detection capability [65–67]. Chen et al. chose carboxyl group-functionalized porphyrin as a ligand, and a porphyrin-based MOF (nPCN-224) nanosphere was applied as a PEC probe for a “signal-on” PEC immunosensor [68]. The intrinsic structural porosity of nPCN-224 provides the advantage for reactant accessibility, facilitating the photoelectric reaction and enabling the sensor to exhibit excellent analytical performance. Based on their porosity, MOFs can effectively encapsulate electron donors for the construction of ultrasensitive PEC sensor. Liu et al. proposed an aptamer-functionalized MOF to load electron donors, and a PEC biosensor was constructed. Conformational changes triggered by target recognition by aptamer sequences and cyclic amplification assisted by T7 exonuclease opened the pores of MOF to release a large number of electron donors, resulting in significantly increased photocurrent [69]. Rani et al. used Zr-MOF loaded AuNPs as nanoprobes to construct a PEC biosensor [70]. The synergistic effect of the electroactive AuNPs and porous Zr-MOF endow the sensor with good catalytic activity and rapid electron transfer kinetics.

Despite this significant advancement, PEC sensing based on intrinsic MOFs still has poor conductivity and a large energy gap, resulting in slow interfacial redox reactions and insufficient energy utilization [71,72]. The introduction of semiconductor materials into MOFs is an emerging route for improving the MOF conductivity and band struc-
ture. Semiconductors, such as TiO\textsubscript{2}, g-C\textsubscript{3}N\textsubscript{4}, CdS and others, and noble metal NPs, such as AuNPs and AgAu nanoshells, have been used to load MOFs to construct sensitive PEC sensors, as shown in Figure 6 [73–77].

Figure 6. (a) Illustration of the principle for PEC detection of alkaline phosphatase activity. Reprinted from Ref. [75] with permission by Royal Society of Chemistry. (b) Synthetic procedure of AgAu/ZIF-8@ZnS@CdS. Reprinted from Ref. [76] with permission by Elsevier.

2.2. MOF-Based Nanoenzymes

Natural enzymes can specifically catalyze chemical reactions under mild conditions; however, they are easily affected by harsh environments and have low stability and high cost. Therefore, artificial enzyme mimics that can compensate for the defects of natural enzymes, particularly nanoenzymes, have attracted extensive attention. The unsaturated metal active sites and the channel confinement effect endow MOFs with enzymatic activity, which has attracted extensive attention in catalysis. Furthermore, the structural diversity, customizable pores, and hydrophobic coordination environment provided by channels make MOFs suitable for replacing natural enzymes.

The MIL series of MOFs (MIL-101(Fe) and MIL-53(Fe)) has been widely used as nanoenzymes for signal amplification in sensors [78–80]. However, the inherent chemical instability and low mimetic enzyme activity of MOFs hinder their application in mimetic enzyme reactions. Li et al. demonstrated a metal-MOF synergistic catalytic strategy by loading platinum nanoparticles (PtNPs) onto MIL-88B-NH\textsubscript{2} (Fe-MOF) to induce electron transfer from Pt to Fe to accelerate the Fe\textsuperscript{3+}/Fe\textsuperscript{2+} redox cycle, improving the overall efficiency of peroxidase-like reactions [81]. Furthermore, a PtNPs-loaded Cu-MOF (Cu-MOF@Pt) was reported, which exhibited a stronger affinity to tetramethylbenzidine (TMB) and H\textsubscript{2}O\textsubscript{2} than horseradish peroxidase [82].

The oxidase-like activity of MOF also plays an important role in sensors. Wang et al. reported a bifunctional MOF (UiO-66-NH\textsubscript{2}@Ce) with excellent oxidase mimicking activity and fluorescence properties [83]. The oxidase-like activity of UiO-66-NH\textsubscript{2}@Ce was attributed to the oxidase-like active Ce\textsuperscript{4+}/Ce\textsuperscript{3+} sites. Based on this, a fluorescent colorimetric dual-channel method was established for the detection of butyrylcholinesterase. The oxidase-like activity of a manganese ion-modified porphyrin MOF (PCN-224-Mn), which can catalyze the conversion of dissolved oxygen to O\textsubscript{2}•\textsuperscript{-} radicals and can further oxidize TMB to oxTMB was demonstrated [84].

With sensor sensitivity developments, MOFs with dual enzymatic activities have also emerged. Luo et al. proposed a mixed-valent Ce-MOF (Ce-BPyDC) that exhibited oxidase and peroxidase-like activities, as depicted in Figure 7a [85]. Ce(III) and Ce(IV) were retained in the Ce-BPyDC structure. The redox activity of Ce(III)/Ce(IV) allowed Ce-BPyDC to exhibit catalytic activity beyond that of horseradish peroxidase and other
MOF nanoenzymes. Shen et al. reported boric-acid-modified MIL-100(Fe) (MIL-100(Fe)-BA), which not only exhibited oxidase and peroxidase-like activities but also provided abundant bioenzyme immobilization recognition sites. A multi-enzyme cascade nanoplatform with high cascade activity, excellent stability, and high sensitivity was constructed by combining MIL-100(Fe)-BA with bioenzymes [86].

In addition to the peroxidase and oxidase activities, MOFs also possess superoxide dismutase (SOD)-like properties. A bimetallic MOF (MOF-818) that mimics Cu/Zn-SOD was designed, as shown in Figure 7b [87]. The SOD-like MOF-818 showed good stability during heating, organic solvents treatments, and denaturation. Based on this catalytic mechanism, a MOF-818-based colorimetric sensing platform for the detection of phosphorylated peptides and proteins was reported. In another study, Cu-TCPP MOF nanodots (CTMDs) were prepared, which could functionally and structurally mimic SOD. CTMDs has a Cu active site coordination environment similar to that of native SOD and an ordered channel similar to the substrate, exhibiting the highest SOD-like activity among the nanozymes [88].

![Figure 7](image)

Figure 7. (a) Scheme of peroxidase-like and oxidase-like activities of Ce-BPyDC. Reprinted from Ref. [85] with permission by American Chemical Society. (b) The bimetallic metal-organic framework platform for mimicking Cu/Zn-superoxide dismutase. Reprinted from Ref. [87] with permission by American Chemical Society.

2.3. MOF-Based Nanocarriers

Molecular recognition elements (proteins, enzymes, nucleic acids and antibodies) and signal amplification elements (enzymes or metal nanoparticles) are essential bio-sensor components. However, scientific, and technological developments, have gradually highlighted the problems with traditional biosensors. For example, the coverage of bioactive substances was low, the direct use of a signal probe led to an unstable output signal, the stability of the enzyme in the existing matrix required improvement, and metal nanoparticles tend to aggregate in catalytic reactions because of their high surface energy. To solve these problems, a large number of nanomaterials have emerged, and MOFs stand out among the hundreds of materials. The high porosity of MOFs enables them to accommodate a large number of active molecules, and the abundant surface functional groups provide opportunities for biomolecular modification.

Attaching signal molecules to MOFs can effectively immobilize signal molecules to the biosensor and enhance the stability of the output signal [89,90]. Furthermore, the encapsulation of metal nanoparticles in MOFs can not only avoid agglomeration, but can also increase the number of metal nanoparticles at each site, thereby enhancing the sensor signal. Yan et al. constructed an ECL sensor by encapsulating bimetallic nanoparticles in Uio-66 (Au&Pt@Uio-66), and Au&Pt@Uio-66 could not only provide multiple catalytic sites for the reaction but could also accelerate the electron transfer efficiency at the electrode interface. The proposed sensor exhibited excellent stability and sensitivity [91]. In biosensors, MOFs as nanocarriers also plays a role in the enrichment of signal tags to improve sensitivity. Zhong et al. reported that CdS QDs were used as signal tags for
electrochemical detection of *Escherichia coli* (*E. coli*) [92]. In the presence of CdS QDs, ZIF-8 was grown in-situ, and the QDs were encapsulated in ZIF-8 to form CdS@ZIF-8. Anti-*E. coli* antibodies were modified on the surface of the ZIF-8 to specifically recognize *E. coli*. Because of the large amount of QDs enriched by ZIF-8, the signal tag labeled on each *E. coli* was greatly enhanced, and the sensitivity of an immunobiosensor using CdS@ZIF-8 as a signal tag was 16 times higher than that of immunobiosensor using CdS quantum dots (QDs). Environmental changes, such as changes in temperature, pH and solvents, often result in reduced enzyme activity. Encapsulating enzymes in MOFs not only improves the enzyme stability but also prevents the degradation of enzymes by proteolytic enzymes in biological matrices. Zhu et al. encapsulated glucose oxidase in ZIF-8 (ZIF-8/GOx), and after immersion in ethanol for 30 min, the free GOx was almost completely inactivated, while the ZIF-8/GOx retained more than 97% activity [93]. Moreover, GOx integrated into ZIF-8 (GOx@ZIF-8) endows the microRNA sensing platform with good storage stability [94].

A specific recognition element is an essential sensor component. To improve the selectivity of sensors, aptamers [95–97], antibodies [98,99], peptides [100,101] and other specific recognition units [102] can be adsorbed on the MOF through covalent bonding, π-π stacking, hydrogen bonding and other actions. The introduction of specific recognition elements provides excellent accuracy for biomacromolecule detection on complex substrates. High-performance sensing platforms require high specificity, stability, sensitivity, accuracy and precision. The intrinsic properties of MOFs enable them to serve as signal probes, nanoenzymes or nanocarriers for sensor construction, and play an important role in enhancing sensor performance.

3. Application of MOFs in Biomacromolecule Sensing

MOFs have gained increasing interest in biomacromolecule sensing owing to their porosity, topological tenability, excellent loading capacity and catalytic properties. The functions of MOFs in a single biosensor are generally diverse. This section discussed the typical applications of MOFs for sensing proteins/peptides, DNA, RNA and polysaccharides, as shown in Table 2.

**Table 2. Applications of MOFs in biomacromolecule sensing.**

| MOFs          | Analytes                  | Methods                  | Limit of Detection | Samples       | Ref. |
|---------------|---------------------------|--------------------------|--------------------|---------------|-----|
| Sm-MOF        | Carcinoembryonic antigen  | Electrochemistry          | 0.001 U mL⁻¹       | Human serum   | [103]|
| Zr-MOF        | Prostate specific antigen | Photoelectrochemistry    | 0.2 pg mL⁻¹        | Human serum   | [104]|
| CD-MOF@Ru(bpy)₂⁺ | Cytokeratin 19 fragment antigen 21-1 | Electrochemiluminescence | 0.006 ng mL⁻¹     | A549 lung cancer cells | [98]|
| His-MIL-101   | Metallothioneins          | Colorimetry              | 10.49 nM           | Human serum   | [79]|
| Zr₁₂-ADB MOF  | Mucin 1                   | Electrochemiluminescence | 0.25 fg mL⁻¹       | Human serum   | [43]|
| RuMOFNSs      | Cardiac troponin I        | Electrochemiluminescence | 0.48 fg mL⁻¹       | Human serum   | [45]|
| MIL-53(Fe)    | Alkaline phosphatase      | Colorimetry              | 0.02 U L⁻¹         | human plasma  | [80]|
| Ru-PEI-L-lys-ZIF-8 | Thrombin                 | Electrochemiluminescence | 0.02 aM            | Serum          | [26]|
| NH₂-MIL-88    | Neuron-specific           | Electrochemiluminescence | 31.6               | Human serum   | [28]|

[92] Reference: M. Zhu et al., *Chemosens.* 2022, 10, 412.
3.1. Application of MOFs in Proteins/Peptides Sensing

Proteins are the main undertakers of life activities. An abnormal protein content in bodily fluids usually indicates the occurrence of diseases. Therefore, sensitive, and accurate, detection methods are of great significance for precision medicine. Owing to their excellent performance, MOFs play an important role in improving the sensitivity, selectivity and stability of protein/peptides sensing. Non-enzymatic protein sensing usually requires specific recognition elements (aptamers or antibodies). MOFs are often used as nanocarriers to immobilize specific recognition elements and can also perform multiple functions. For example, Zhao et al. constructed an ECL sensor using MOFs as signal probes and antibody nanocarriers (Figure 8) [112]. Using tris(2,2’-bipyridyl)-ruthenium(II) encapsulated in a 3D Zn-based MOF as the electron donor and gold nanoparticle-loaded NiFe-based MOF as the electron acceptor, the sensitive detection of amyloid-β was achieved through the resonance energy transfer between the two MOFs. MOF can also act as a nanoenzyme for protein sensing. Wang et al. constructed a colorimetric sensor for antigen detection using Cu-MOF as an antibody carrier and nanozyme [113]. Owing to the excellent catalytic activity of the MOFs, the sensitivity of the Cu-MOF-labeled antibody toward the antigen was three times higher than that of the horseradish peroxidase-labeled antibody.
The intrinsic catalytic activity of enzymatic proteins is another concept for constructing biosensors. Persistent pores inside the MOFs facilitate the pre-enrichment of guest molecules and increase the guest-host interactions for more sensitive chemical sensing. Sha used ZIF-8 as a nanocarrier of the oxidant (MnO₂) and signal probe (o-phenylenediamine). The interactions between MnO₂ and o-phenylenediamine, MnO₂ and tiopronin, and tiopronin and alanine aminotransferase changed the fluorescence emission, causing the sensing of alanine aminotransferase to present ternary visualization [114]. Because of the hydrolysis of pyrophosphate ions (PPi) by acid phosphatase (ACP), a PPi-mediated fluorescence-tuned ACP sensing based on the NH₂-MIL-101/o-phenylenediamine/H₂O₂ system was constructed. NH₂-MIL-101 acted as both a fluorescent indicator and biomimetic catalyst in the proposed sensor, and ACP in serum samples was successfully detected [115].

The particularity of the protein structure renders the electron transfer efficiency between the protein and substrate insufficient to meet the requirements of practical detection. Taking electrochemical sensing as an example, the enrichment of proteins on an electrode usually leads to an increase in the electrochemical impedance of the electrode, preventing electron transport. A Ni-MOF-based electrochemical sensor was reported, and a Ni-MOF assembled with redox-active ligands was employed as an electrochemical signal probe and nanocarrier for thrombin (Tb) detection [116]. The introduction of Ni-MOF improved the electron transport efficiency of the electrode, as shown in Figure 9.
Figure 9. (A) Scheme of the preparation of AP II bioconjugate signal probe; (B) the magnetic and electrochemical properties of Ni-MOF; (C) fabrication process of the electrochemical aptasensor for Tb detection. Reprinted from Ref. [116] with permission by Elsevier.

Additionally, Biswas et al. investigated the electrochemical properties of Sm-MOF synthesized using three different organic ligands, namely, trimesic acid, meso-tetra(4-carboxyphenyl) porphyrin, and 1,3,6,8-tetra(4-carboxyphenyl) pyrene. The results showed that all three Sm-MOFs had excellent electron transport efficiency and good electrocatalytic activity. Sm-MOF is not only a nanoenzyme but also a nanocarrier for antibody immobilization, and the Sm-MOF-based immunosensor has been successfully used to detect carcinoembryonic antigen in human serum samples, as depicted in Figure 10a [103]. Zhang et al. developed a novel enzyme-free PEC immunoassay based on DNA-mediated nanoscale zirconium porphyrin MOFs (NMOFs) for the ultrasensitive detection of prostate-specific antigen (PSA), as depicted in Figure 10b [104]. The linear range of the sensor was 1 pg mL$^{-1}$ to 1 ng mL$^{-1}$ with a limit of detection of 0.2 pg mL$^{-1}$, which was attributed to the DNA mediator NMOF nanoprobes with excellent electron transport efficiency and PEC activity as well as the high antibody loading of NMOFs.

Figure 10. (a) Illustration for Sm-MOF-based immunoassay fabrication. Reprinted from Ref. [103] with permission by American Chemical Society. (b) Illustration for DNA-mediated NMOFs-based PEC immunoassay. Reprinted from Ref. [104] with permission by American Chemical Society.
Active peptides mainly control human growth, development, immune regulation, and metabolism, and are in a state of balance in the human body. If an active peptide is reduced, human body functions undergo significant changes. For example, amino-terminal pro-B-type natriuretic peptide (NT-proBNP), in the family of natriuretic peptides synthesized and secreted by cardiomyocytes, is an emerging biomarker for the diagnosis of heart failure. The serum natriuretic peptide level is related to age, and the severity of heart failure is proportional to the serum NT-proBNP level [117]. Liu et al. developed a sandwich-type electrochemical immunosensor. The secondary antibody-labeled Cu-MOF was used as the signal probe, and NT-proBNP analysis in clinical serum samples was successfully conducted [105].

3.2. Application of MOFs in DNA Sensing

DNA sensing can not only predict disease risk and avoid or delay the occurrence of disease but can also diagnose potential genetic diseases in fetuses. The signal molecules or recognition elements in the sensor are unstable under harsh conditions, and the MOF, as a protective layer, is beneficial for protecting the sensing ability of the sensor. For example, in surface-enhanced Raman scattering sensing, MOF coatings can effectively prevent damage to DNA receptors and signaling probe structures from oxidation, sulfidation, and enzymatic degradation [118]. To prevent the signal probe from being affected by the external environment, it is common to directly encapsulate signal molecules with MOFs to form MOF-based nanoprobes. Based on the complementary base pairing of DNA, the target DNA is often used as a response element to trigger the release of signaling molecules. A MOF-based nanoprobe was prepared using porous MOF as a scaffold to load signaling dyes and a DNA hairpin as capping shells [106]. Once the target was introduced, a competitive displacement reaction triggered the release of the fluorophore from the MOF pores, as shown in Figure 11a. Therefore, a significantly enhanced fluorescence signal was observed owing to the high loading capacity of the MOFs. Thus, stimuli-responsive nanoprobes can sensitively detect DNA targets with a low detection limit of 20 fM and can selectively recognize single-base mismatches. A homogeneous electrochemical DNA sensor was reported for the simultaneous detection of mecA and nuc genes in *Staphylococcus aureus*, as shown in Figure 11b [119]. MOFs (UiO-66-NH$_2$) were used as nanocarriers. The electroactive dyes were individually encapsulated in UiO-66-NH$_2$ and locked using a hybrid double-stranded DNA (ds-DNA). Based on the target-responsive electroactive dye release strategy, once the target DNA is present, it fully hybridizes to the displaced DNA. Thus, the DNA was displaced from the MOF surface, resulting in the release of electroactive dyes.

![Figure 11](image-url)
Additionally, MOF can be used directly as signal probes for DNA detection. Wang et al. proposed a co-reactant-free biosensor using MOF as a signal probe for the ultrasensitive detection of the breast cancer 1 gene [107]. In the presence of cetyltrimethylammonium bromide (CTAB), chelated zinc ions and carboxyl-rich tris(4,4′-dicarboxy-2,2′-bipyridyl)ruthenium(II) formed a novel flower-like ZnMOF(Ru). The presence of CTAB prevented the deposition of nanocomposites and proton attack in the aqueous system, which greatly improved the luminescence efficiency of the ZnMOF(Ru). Owing to the enhanced synergy, the ECL signal was amplified 53-fold in the co-reactant-free system.

The formation of G-quadruplexes (G4) in human telomeric DNA has been demonstrated to inhibit telomerase activity, which is associated with the proliferation of many cancer cells. Therefore, the G4s have become recognized targets for anticancer therapeutic strategies. In recent years, the development of a simple and selective G4 structure detection platform has become an important research topic. Owing to the specific interaction between G4 and hemin, a fluorescent cerium-based MOF coupled with hemin (hemin@Ce-MOF) has been used to detect human telomeric DNA [108]. The G4 structure of human telomeric DNA can compete with MOF for hemin, restoring the fluorescence of hemin and realizing target-responsive signal output.

In addition to being used as signal probes or nanozymes to facilitate signal output, MOFs can also be used as quenchers for the construction of “signal on” sensors. Liang et al. developed a universal fluorescent biosensor for detecting the Mycobacterium tuberculosis-specific insertion sequence IS6110 gene fragment [120]. A novel two-dimensional MOF (Cu-TCPP) was used as the acceptor and CdTe QDs-labeled single-stranded DNA (ssDNA) (QDs-DNA) was used as the donor. Cu-TCPP has a higher affinity for ssDNA than for dsDNA. In the absence of a target, the fluorescence of the QDs-DNA was quenched due to the π–π stacking interaction between Cu-TCPP and ssDNA. Otherwise, the QDs-DNA hybridizes to the target to form a duplex, and fluorescence is maintained in a target-concentration-dependent manner. In another study, a switchable fluorescent biosensor for the simple and efficient detection of nucleic acid biomarkers was developed using 6-carboxyfluorescein (FAM)-modified ssDNA as a probe (FAM-P1/P2) and zirconium porphyrin MOFs nanoparticles (ZrMOFs) as fluorescence quenchers [121]. Since the adsorption capacity of ZrMOF for ssDNA is better than that for dsDNA, the fluorescence signal switched from “off” to “on”, enabling rapid and ultrasensitive detection of DNA and RNA within 30 min.

3.3. Application of MOFs in RNA Sensing

Viral diseases are usually contagious, and timely detection and diagnosis can help prevent and control them. Some diseases caused by RNA viruses (such as hepatitis B, hepatitis C, HIV and SARS-CoV-2) can be detected, treated and controlled early through RNA detection. Therefore, it is important to develop more sensitive and economical RNA detection methods for the diagnosis and prevention of diseases. Multiple interactions (π–π stacking, electrostatic interaction, hydrogen bonding and others) between MOFs and DNA/RNA have increased the attention on MOFs for RNA detection. Using zwitterionic copper (II) MOF (MOF1) as a quencher, Chen et al. constructed a fluorescent sensor for Ebola virus RNA detection through π–π stacking and electrostatic interactions between MOF and DNA probes, as shown in Figure 12a [122]. In the presence of targeted Ebola virus-conserved RNA sequences or Ebola virus-encoded miRNA-like fragments, fluorophore-labeled DNA (P-DNA) hybridized to the analyte to generate a P-DNA@RNA biphasic. P-DNA was released from MOF 1, which triggered fluorescence recovery. Simultaneous detection of the two target RNAs was achieved by single and simultaneous fluorescence analysis. In another study, an ultrasensitive switchable ECL RNA sensing platform was established using a metal-organic gel (MOG) and MOF (Fe-MIL-88) as electrode substrates and nanotags, respectively [109]. Fe-MIL-88 was not only an ECL acceptors in ECL resonance energy transfer systems, but also possessed metal active
centers to deplete co-reactants to trigger the double-quenching effect on the ECL of MOGs. The ECL platform exhibited a wide detection range (0.3 nM to 3 μM) for Zika virus RNA detection with a detection limit as low as 0.1 nM.

miRNAs in the human body are involved in various biological and pathological processes. Their dysregulated expression is often associated with multiple types of cancer; therefore, they are widely used as important biomarkers for cancer diagnosis and treatment. In recent years, MOF-based biosensors have been applied in the field of miRNA analysis. Chang et al. prepared functionalized MOFs using porous Uio-66-NH$_2$ as a nanocarrier loaded with electroactive dyes and dsDNA as a shield. The simultaneous detection of multiple RNAs (let-7a and miRNA-21) was achieved by loading different electroactive dyes and dsDNA, as shown in Figure 12b [123]. The detection of miRNAs in living cells remains challenging because of their low abundance, small size, facile degradability, and sequence similarity. Therefore, high-specificity and high-sensitivity miRNA sensing are particularly important. Based on the interaction between thiazole orange and rhodamine B molecules, Han et al. developed a ratiometric fluorescent probe based on DNA-functionalized MOFs [124]. Based on this ratiometric fluorescent probe, the picomolar limit of detection (57 pM) of miRNA-21 was obtained without signal amplification. After penetrating cells, intracellular miRNA-21 can also be imaged by the strand displacement reaction, distinguishing cancer cells from normal cells.

![Figure 12](image)

**Figure 12.** (a) Scheme for simultaneous detection of two Ebola virus-related sequences by an efficient fluorescence sensing platform based on MOF 1. Reprinted from Ref. [122] with permission by Elsevier. (b) Principle of multiplex detection of miRNAs in a MOF-based electrochemical biosensor. Reprinted from Ref. [123] with permission by American Chemical Society.

### 3.4. Application of MOFs in Polysaccharide Sensing

Human physiological and pathological processes are regulated by several factors. Polysaccharides (heparin (Hep), chondroitin sulfate (CS) and others, mostly regulate immunity and suppress tumors in the human body, but they also delay aging and reduce blood sugar levels. Hep plays an important role in the regulation of normal physiological and pathological processes, including metabolism, immune defense, cell growth and differentiation, venous thromboembolism, inflammation and blood coagulation. Moreover, since the early 20th century, Hep has been used as an anticoagulant in clinical
diagnostic and therapeutic procedures, particularly in open-heart surgery [125–127]. Recently, a terbium MOF/bovine serum albumin-capped gold nanocluster double-emission reverse-change ratio fluorescence nanoplatform was designed for the colorimetric fluorescence sensing of Hep and CS, as shown in Figure 13 [110]. The sensor exhibited high precision and sensitivity for Hep and CS because the dual-emission ratio fluorescence signal could deduct the fluctuation of the environment through self-correction and possessed an intrinsic signal amplification function. Additionally, the colorimetric detection of Hep and CS can be accomplished by reading the RGB information from a smartphone. The sensor was applied to the quantitative detection of Hep and CS in human serum samples with satisfactory recovery.

![Figure 13. The dual-emission reverse change ratio fluorescence nanoplatform for fluorimetric (A) and colorimetric (B) sensing of Hep and CS. Reprinted from Ref. [110] with permission by Elsevier.](image)

Lipopolysaccharide (LPS) is the main component of the outer membrane of gram-negative bacteria. LPS can cause febrile reactions, microcirculatory disturbances, septic shock and vascular coagulation. Therefore, sensitive detection of LPS is particularly important in the fields of food safety, therapy and medicine. Duan et al. developed an electrochemical aptasensor for LPS with Cu-MOF as the signal probe. [111] The aptamers immobilized on the electrodes could specifically bind to LPS. The specific interaction of the LPS carbohydrate moiety with the anionic groups of Cu-MOF enabled the MOF to be labeled on the electrode surface. The electrochemical signal could be directly measured by the electrochemical redox reaction of Cu(II)/Cu(I) in the Cu-MOF. This electrochemical aptamer sensor exhibited a low detection limit (0.29 pg mL$^{-1}$) and was successfully applied for the detection of LPS in water samples.

4. Summary and Future Perspectives

The high porosity, tunable topology and easy functionalization of MOFs make them suitable for various biomacromolecular sensing applications. The combination of MOFs with other nanomaterials (such as, g-C$_3$N$_4$, AuNPs, PtNPs and others) produces a synergistic effect in biomacromolecular sensing. The structure and properties of MOFs can be engineered by changing the organic ligands or metal clusters. MOFs often play multiple roles in biosensors such as nanoprobe, nanozymes and nanocarriers.
Although significant progress has been made in biomacromolecular sensing, the challenges of MOF-based biosensors are gradually emerging, and more efforts are required to overcome these defects to improve the performance of MOF-based sensors. Rigid MOFs often have just one specific structure, which cannot adapt to different chemical reactions by changing the structure according to the environment. Biomacromolecular sensing usually requires excellent reproducibility and MOFs do not have sufficient chemical stability to enable multiple reactions. Metal ions or organic ligands in MOFs are easily leached into biosensing systems, resulting in low biocompatibility. Moreover, the frameworks of some MOFs are prone to collapse in aqueous media, which cannot meet the requirements for the long-term continuous monitoring of biomolecules. The development of stable, low-toxicity, biocompatible and flexible MOFs is key to improving the reproducibility of MOF-based biosensors. On the other hand, the porosity of most reported MOFs are micropores, which limits their application in diffusion-limited processes. Owing to the restricted accessible sites provided by MOFs, the functionalization of MOFs with other nanomaterials or biomolecules through post-modification processes usually occurs on the surface of MOFs, and the internal pore structure and surface is not available for practical utilization. The development of advanced synthetic strategies to increase the accessible active sites of MOFs is crucial for enhancing the performance of MOF-based biosensors.

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