

Metal-Organic Frameworks in Biomedical Applications: Drug Delivery, Medical Imaging, and Biosensing

Mingqing Li*

Biology-BioTech, Biology Department, Hong Kong Baptist University, 999077 Hong Kong, China

Abstract. Metal-organic frameworks (MOFs) and their nanoscale counterparts (NMOFs) represent a transformative class of hybrid porous materials that have rapidly ascended to the forefront of biomedical research. Their unique confluence of structural and chemical properties renders them exceptionally versatile platforms for advanced therapeutic and diagnostic applications. This comprehensive review critically examines and synthesizes recent, groundbreaking progress in three pivotal biomedical domains: intelligent drug delivery systems, multimodal medical imaging, and high-performance electrochemical biosensors. I delve into the fundamental structure-property relationships that underpin MOF functionality, showcasing how rational design at the molecular and nanoscale levels enables the creation of stimuli-responsive carriers for targeted therapy, integrated contrast agents for multi-technique diagnostics, and sensitive interfaces for biomarker detection. By analyzing exemplary studies, from pH-sensitive, self-indicating drug carriers to theranostic nanoprobe capable of simultaneous imaging and treatment, this article elucidates the convergent advantages and design principles of MOF-based technologies. Furthermore, I provide a balanced discussion on the persistent translational challenges—such as long-term biocompatibility, scalable synthesis, and in vivo fate—and propose informed perspectives on future research directions. The continuous convergence of coordination chemistry, materials science, and biology firmly positions engineered MOFs as cornerstone materials for the development of next-generation precision nanomedicine and point-of-care diagnostic platforms.

1 Introduction

The relentless pursuit of precision in medicine—aiming to deliver the right treatment, to the right location, at the right time—has fueled an insatiable demand for smarter, more adaptable biomedical materials. Conventional platforms, from liposomal drug carriers to small-molecule contrast agents, often grapple with intrinsic limitations: insufficient loading capacity, lack of controlled release, poor stability, low sensitivity, and non-specific biodistribution. The emergence of metal-organic frameworks (MOFs) offers a paradigm-shifting solution to these multifaceted challenges. MOFs are crystalline, porous materials

* Corresponding author: 22257918@life.hkbu.edu.hk

constructed from the self-assembly of metal ions or clusters (acting as nodes) and polytopic organic linkers (serving as struts). This modular architecture is not merely a structural novelty; it is the foundation of their functional genius [1, 2].

When engineered at the nanoscale (as NMOFs), these materials retain their crystalline order and porosity while acquiring characteristics essential for biological interaction: colloidal stability, injectable sizes, and improved tissue penetration. The biomedical promise of MOFs is inherently dualistic. First, it lies in their intrinsic structural assets: permanent nanoscale pores create vast, accessible surface areas for guest molecule encapsulation, while their crystalline nature ensures batch-to-batch reproducibility and predictable diffusion pathways. Second, and perhaps more powerfully, it stems from their limitless designability. Virtually every component is tunable: the metal node can be selected for its catalytic, magnetic, or radiographic properties; the organic linker can be chosen for its flexibility, hydrophilicity, or inherent fluorescence; and the entire structure can be post-synthetically modified with polymers, targeting ligands, or other functional groups [3, 4].

This review articulates how this powerful combination is being harnessed across three interconnected frontiers of biomedicine. In drug delivery, MOFs evolve from passive reservoirs into intelligent systems capable of sensing their microenvironment and releasing therapeutics on demand [5]. In medical imaging, they transcend single-modality agents to become integrated, multi-modal diagnostic platforms that provide complementary information. In biosensing, they overcome the limitations of traditional electrodes by offering highly organized, stable, and catalytic interfaces that dramatically enhance sensitivity and selectivity [6, 7]. By examining these trajectories, I highlight the unifying principles of MOF-based design while acknowledging the hurdles that must be cleared to translate these remarkable materials from the laboratory bench to the clinical bedside.

2 Structural and functional foundations of mof versatility

The remarkable adaptability of MOFs in diverse biomedical roles is not serendipitous but is fundamentally rooted in a direct and exploitable structure-function relationship. This relationship is built upon two interdependent pillars: innate structural advantages and a nearly limitless capacity for functionalization.

2.1 Intrinsic structural advantages

The defining characteristic of MOFs is their extreme porosity. NMOFs typically exhibit surface areas ranging from hundreds to thousands of square meters per gram, far exceeding those of mesoporous silica or polymeric nanoparticles. This porosity is not random; it is regular, crystalline, and often tunable in size from micro- to mesopores. This provides an enormous internal volume and surface for the adsorption and encapsulation of therapeutic drugs (e.g., chemotherapeutics, genes), imaging agents (e.g., dyes, radioisotopes), or enzymatic biosensors. The high loading capacity that results is a primary driver for their use, maximizing therapeutic or diagnostic payload per particle. Furthermore, the rigid, well-defined pore structures can protect sensitive biomolecular cargos (like DNA or proteins) from enzymatic degradation, while the nanoscale dimensions promote cellular uptake via endocytic pathways.

2.2 The functionalization paradigm: engineering "smartness"

The true transformative power of MOFs lies in their synthetic plasticity, or "designability." This enables the systematic engineering of advanced functionalities, and MOFs' designability mainly shows in the following 3 aspects:

2.2.1 Stimuli-responsiveness

The framework chemistry can be designed to be labile under specific biological conditions. For instance, Zn²⁺-imidazolate bonds in ZIF-8 are stable at physiological pH but rapidly dissociate in the acidic tumor microenvironment (pH~6.5), providing an intrinsic pH-responsive drug release mechanism. Similarly, linkers with disulfide bonds can be cleaved in the reductive cytoplasm, and azo-based linkers can be severed by overexpressed enzymes like azoreductase in the gut.

2.2.2 Targeting ability

The external surface of NMOFs can be grafted with targeting moieties such as folic acid, peptides (e.g., RGD), antibodies, or aptamers. This active targeting leverages the specific overexpression of receptors on diseased cells (e.g., folate receptors on many cancers) to enhance particle accumulation at the desired site, reducing off-target effects and required dosages.

2.2.3 Inherent signaling capabilities

The building blocks themselves can be functional. Using luminescent lanthanide ions (Tb³⁺, Eu³⁺) as nodes or aromatic, fluorogenic linkers (like tetraphenylethylene) integrates stable fluorescence directly into the scaffold. Paramagnetic metals like Gd³⁺ or Mn²⁺ impart MRI contrast properties. This eliminates the need for physical encapsulation of signaling molecules, which often leak or quench.

These above synergistic foundation, where a robust, high-capacity porous scaffold is seamlessly fused with customized chemical intelligence, empowers the sophisticated applications detailed in the following sections.

3 MOFs in drug delivery: from passive carriers to "self-indicating" therapeutics

The journey of MOFs in drug delivery mirrors the evolution of the field itself, from simple, passive diffusion-based release to complex, active targeting and feedback-controlled systems

3.1 Strategies for enhanced delivery and targeting

Early proof-of-concept studies demonstrated the superior loading of drugs like doxorubicin or cisplatin into MOF pores. Contemporary research focuses on sophisticated control. Biomimetic mineralization, such as coating a drug-loaded ZIF-8 core with a hydroxyapatite shell, serves a dual purpose: it seals the drug at neutral pH but allows release in acidic bone-tumor regions while promoting osteointegration. Surface engineering with stealth polymers like polyethylene glycol (PEG) prolongs circulation time, while subsequent conjugation of targeting ligands (e.g., folic acid) guides the carrier to specific cells. Furthermore, the ability

to co-load multiple drugs within the same MOF particle enables synergistic combination therapy with ratiometric control [8].

3.2 The pinnacle: "self-indicating" and feedback-enabled systems

A groundbreaking study on fluorescent, hollow MOF nanotubes exemplifies the cutting edge. Here, the MOF was constructed from a Zr cluster and a tetraphenylethylene dicarboxylate linker, which conferred inherent, aggregation-induced emission (AIE) fluorescence. The synthesis yielded hollow nanotubes, providing an ultrahigh doxorubicin (DOX) loading capacity of 36.5 wt%. The system operated on two intelligent levels: The first level is that MOF has a good controlled release property in pH, discharging 70% of DOX at pH 5.0 (simulating endosomes/lysosomes) versus only 27.7% at pH 7.4, ensuring targeted cytotoxicity in cancer cells. The second level is that the Real-Time Feedback shows the loaded DOX quenched the MOF's fluorescence via Forster resonance energy transfer (FRET). As DOX was released in acidic conditions, the MOF's fluorescence recovered. This allowed for real-time, visual monitoring of drug release kinetics inside live cells using confocal microscopy, transforming the carrier into a "self-indicating" therapeutic that reports its own operational status.

4 MOFs in medical imaging: enabling multimodal and theranostic platforms

The modular composition of MOFs allows for the rational incorporation of diverse imaging agents, moving beyond simple contrast enhancement to integrated diagnostic solutions.

4.1 Serving as multimodal imaging hubs

Different imaging techniques provide complementary information, and MOFs are ideal vessels to combine them. A single NMOF particle can be engineered to contain: MRI Agents (Gd^{3+} , Mn^{2+}), CT Agents (Hf^{4+} , Zr^{4+}), Optical Agents (fluorescent linkers), and Nuclear Agents (^{64}Cu , ^{89}Zr). For example, a composite like Au@MIL-88(Fe) combines a gold nanoparticle core (for CT), an iron-based MOF shell (for T2-weighted MRI), and a surface-coated dye (for FI), creating a trimodal nanoprobe. This allows pre-operative tumor localization via MRI/CT and real-time visual guidance during surgery via FI, dramatically improving diagnostic accuracy and surgical outcomes.

4.2 The theranostic paradigm

Theranostics, the fusion of therapy and diagnostics, is perhaps the most compelling application. A MOF can be simultaneously loaded with a chemotherapeutic drug and endowed with MRI contrast capability. This allows clinicians to non-invasively track the nanocarrier's biodistribution, accumulation at the tumor site, and subsequent drug release kinetics in real-time using clinical imaging modalities.

5 MOFs in electrochemical biosensors: creating highly efficient and selective interfaces

Electrochemical biosensors demand interfaces that facilitate efficient electron transfer, high analyte loading, and specific molecular recognition. MOFs, particularly when composited with conductive nanomaterials, are engineered to excel in all these aspects.

5.1 Mechanisms of performance enhancement

Immobilization Matrices and Signal Amplifiers: The porous MOF structure acts as a protective cage for immobilizing enzymes, antibodies, or DNA aptamers, preserving their bioactivity. When conductive 2D MOF nanosheets are decorated with catalytic gold nanoparticles, they create a nanozyme with exceptional peroxidase-like activity. This significantly amplifies the electrochemical signal in the detection of hydrogen peroxide, a key cancer biomarker.

Sensitivity through Porosity and Catalysis: The vast internal surface area of MOFs concentrates target analyte molecules near the electrode surface. Furthermore, metal nodes (e.g., Cu^{2+} , Co^{2+}) or encapsulated metal nanoparticles (e.g., Ag NPs) within the pores provide abundant, well-dispersed catalytic sites for the direct oxidation or reduction of analytes like glucose, eliminating the need for natural enzymes.

Achieving Selectivity: MOF pores can be size-selective, physically excluding larger interferents. More advanced strategies involve post-synthetic modification of the pore walls with molecular recognition elements. For instance, a MOF can be functionalized with a specific aptamer sequence that undergoes a conformational change upon binding to an antibiotic like ciprofloxacin, thereby modulating the electrochemical signal with high specificity [9]. Other works also demonstrate simultaneous detection of biomarkers like ascorbic acid, uric acid, and folic acid [10].

6 Common themes, challenges, and future perspectives

6.1 Colour illustrations

Across drug delivery, imaging, and sensing, the success of MOFs stems from shared virtues: their exceptional loading capacity derived from ultrahigh porosity; their precise chemical tunability enabling custom responses; and their structural robustness allowing for stable performance in biological environments. The common thread is the ability to rationally design a single nanomaterial to perform multiple, complex tasks.

6.2 Persistent challenges for clinical translation

Despite the prolific research output, significant hurdles remain. A paramount concern is ensuring biocompatibility and long-term safety concurrently, the scalable and reproducible synthesis of MOF nanoparticles under Good Manufacturing Practice standards remains a significant hurdle, as many lab-scale protocols rely on complex steps or costly reagents unsuitable for mass production. Furthermore, achieving reliable targeting efficiency *in vivo* presents an intricate obstacle; biological barriers such as rapid protein corona formation, sequestration by the mononuclear phagocyte system, and non-specific accumulation can severely undermine the precision promised by surface-functionalized ligands, limiting therapeutic specificity and efficacy.

6.3 Informed future directions

The trajectory of MOF research points towards two main goals. The first is the advancement of fully biodegradable frameworks using endogenous metal ions (e.g., Fe, Zn) and metabolizable organic linkers. The other involves the pursuit of advanced theranostic integration, engineering sophisticated "all-in-one" platforms that merge multiple therapeutic modalities with multiplexed imaging and real-time biosensing capabilities. The other one is about the critical frontier involves the pursuit of advanced theranostic integration. This entails engineering sophisticated "all-in-one" platforms that move beyond simple drug-plus-imaging combinations. The goal is to seamlessly merge multiple therapeutic modalities-such as chemotherapy, photothermal therapy, and immunomodulation-with multiplexed imaging and real-time biosensing capabilities within a single, unified nanostructure. Such integration aims to enable synergistic treatments and provide immediate feedback on therapeutic response, representing a significant leap toward dynamically adaptive and personalized precision medicine.

7 Conclusion

Metal-organic frameworks have unequivocally demonstrated their vast potential as a cornerstone technology for advanced biomedical applications. Their journey from porous curiosities to multifunctional nanoplatfoms highlights a powerful principle: by mastering the coordination chemistry at the nanoscale, we can engineer materials with prescribed intelligence. In drug delivery, they promise minimized side effects and maximized efficacy through targeted, stimuli-responsive release. In medical imaging, they break down the barriers between modalities, offering clinicians a composite, high-fidelity view of disease. In biosensing, they push the limits of detection, bringing us closer to rapid, accurate point-of-care diagnostics. While the path to widespread clinical adoption is steeped in challenges related to safety, manufacturing, and complex biology, the foundational research laid over the past decade is robust. The continued interdisciplinary collaboration among chemists, materials scientists, biologists, and clinicians will be essential to navigate these challenges. As this synergy strengthens, the vision of deploying tailored MOF-based agents for personalized theranostics and early diagnosis moves steadily from the realm of compelling prospect to tangible reality, heralding a new era of precision medicine.

References

1. M. Chen, R. Dong, J. Zhang, H. Tang, Q. Li, H. Shao, X. Jiang, Nanoscale metal-organic frameworks that are both fluorescent and hollow for self-indicating drug delivery. *ACS Applied Materials & Interfaces* **13**, 18554–62 (2021).
2. F.D. Duman, R.S. Forgan, Applications of nanoscale metal-organic frameworks as imaging agents in biology and medicine. *Journal of Materials Chemistry B* **9**, 3423–49 (2021).
3. M. Parsaei, K. Akhbari, M. Parsaei, K. Akhbari, Synthesis and application of MOF-808 decorated with folic acid-conjugated chitosan as a strong nanocarrier for the targeted drug delivery of quercetin. *Inorganic Chemistry* **61**, 19354–68 (2022).
4. S. Chand, O. Alahmed, W.S. Baslyman, A. Dey, S. Qutub, R. Saha, Y. Hijikata, M. Alaamery, N.M. Khashab, DNA-mimicking metal-organic frameworks with accessible adenine faces for complementary base pairing. *JACS Au* **2**, 623–30 (2022).

5. L. Shi, J. Wu, X. Qiao, Y. Ha, Y. Li, C. Peng, R. Wu, In situ biomimetic mineralization on ZIF-8 for smart drug delivery. *ACS Biomaterials Science & Engineering* **6**, 4595–4603 (2020).
6. Y. Liu, W. Shi, Y. Lu, G. Liu, L. Hou, Y. Wang, Nonenzymatic glucose sensing and magnetic property based on the composite formed by encapsulating AG nanoparticles in cluster-based Co-MOF. *Inorganic Chemistry* **58**, 16743–51 (2019).
7. W. Huang, Y. Xu, Z. Wang, K. Liao, Y. Zhang, Y. Sun, Dual nanozyme based on ultrathin 2D conductive MOF nanosheets intergraded with gold nanoparticles for electrochemical biosensing of H₂O₂ in cancer cells. *Talanta* **249**, 123612 (2022).
8. C. Orellana-Tavra, M. Koppen, A. Li, N. Stock, D. Fairen-Jimenez, Biocompatible, crystalline, and amorphous bismuth-based metal-organic frameworks for drug delivery. *ACS Applied Materials & Interfaces* **12**, 5633–41 (2020).
9. M. Varsha, G. Nageswaran, Ruthenium doped Cu-MOF as an efficient sensing platform for the voltammetric detection of ciprofloxacin. *Microchemical Journal* **188**, 10848 (2023).
10. D.K. Yadav, R. Gupta, V. Ganesan, P.K. Sonkar, Individual and simultaneous voltammetric determination of ascorbic acid, uric acid and folic acid by using a glassy carbon electrode modified with gold nanoparticles linked to bentonite via cysteine groups. *Microchimica Acta* **184**, 1951–1957 (2017).