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REVIEW

Micro- and Nanomotors: Engineered Tools for Targeted and Efficient Biomedicine

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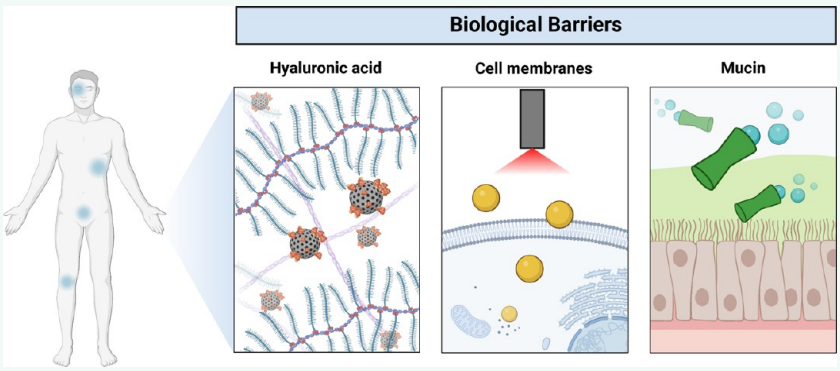

ABSTRACT: **Over the past two decades, nanotechnology has made significant progress toward the development and applications of micromotors (MMs) and nanomotors (NMs). Characterized by their capability to self-propel and swim in fluids, they have emerged as promising tools in various fields, particularly in biomedicine. This Review presents an overview of the current state of MMs and NMs, their motion in viscous media and complex environments, their interaction with biological barriers, and potential therapeutical applications. We identify the choice of appropriate administration routes to reach their target location as a key aspect of the success of MMs and NMs in biomedical applications. Looking ahead, we envision NMs playing a key role in treating diverse medical disorders, as recent proof-of-concept *in vivo* studies demonstrate their distinct capabilities and versatility. However, addressing regulatory, scalability, biocompatibility, and safety concerns remains imperative for the successful translation of NMs into clinical trials and industrial-scale production. This work provides a guideline for researchers, guiding them through the current landscape, challenges, and prospects of using MMs and NMs in biomedicine, thereby encouraging their responsible development and positioning in the future of nanomedicine. Furthermore, we outline critical areas for further research, including studies on biocompatibility, safety, and methods to overcome physical obstacles.**

KEYWORDS: *nanomotors, micromotors, viscous media, biological barriers, biomedical applications, drug delivery, self-propelled particles, target delivery, nanobots, nanomedicine*

1. INTRODUCTION

The field of nanotechnology and nanoengineering has seen remarkable advancements in recent years, particularly in the development and application of micromotors (MMs) and nanomotors (NMs), which have now celebrated two decades of progress (Figure 1).[1−3] MMs and NMs, with their ability to self-propel, have opened new possibilities in various fields[4−6] by exhibiting navigation and smart interactions capabilities within the surrounding media. These properties have enabled MMs and NMs as enhanced nanocarriers compared to passive nanoparticles (NPs), which rely on diffusion and often get trapped in complex media.[7−9] While it is important to understand the mechanisms of motion of MMs and NMs it is also crucial to understand and characterize the interactions between nanomaterials and biointerfaces and how these motors can modulate such interactions for its benefit, thereby enhancing their applicability.

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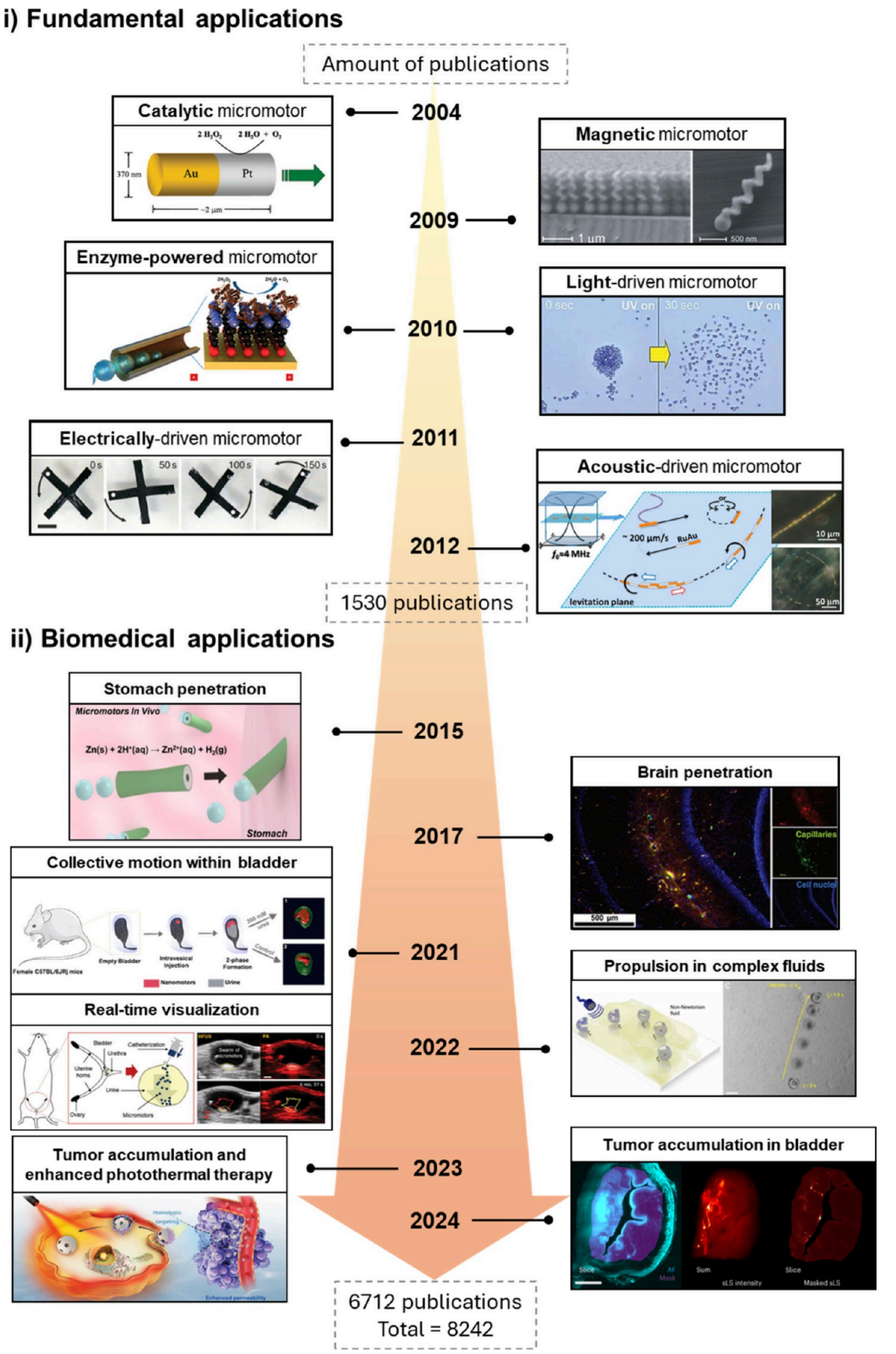

Figure 1. Key evolution publications on the field of MMs and NMs from fundamental studies and biomedical application points of view. Number of papers published in the field from 2004−2012 and 2013 to 2025, with the data obtained from "Web of Science". (i) Fundamental applications: Reproduced or adapted with permission from ref 16. Copyright 2004 American Chemical Society. Reproduced or adapted with

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Figure 1. continued

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Table 1. Summary of MMs and NMs Propelled by Chemical Reactions in Various Biological Media

type of chemically propelled mechanism	type of motor	biological media used	main result	refs
H_2O_2 decomposition − O_2 bubbles	catalase	blood	good motion at physiological conditions	94, 95
H_2 bubbles	Janus MMs: titanium in one side	serum, cell culture media	speed 500 and 1200 μm/s, respectively	97
bubbles Zn-acid reaction	Janus Ga/Zn MMs	gastroenteric acid	383 μm/s	98
H_2 bubbles	PEDOT/zinc or Mg-based MMs	*in vivo* mouse stomach	motion in gastric media and core degradation releasing cargo	100−102
NO	Janus NMs of iron oxide and polydopamine	biofilms	antimicrobial properties, reducing colony formation in burn wounds in *in vivo*	104
H_2O_2 decomposition − O_2 bubbles	PLGA-catalase MMs	culture media	1 mM H_2O_2 required for single particle motion	113
magnetic motion + enzyme	urease-based nanopropellers	mucin gels	enzyme can liquified the mucin gel to enhance motion	114
H_2O_2 decomposition − O_2 bubbles	catalase-based tadpole-like brushes	viscous tumor environment	2 mM of H_2O_2 to propel at 15 μm/s and 10 mM H_2O_2 to propel at 24 μm/s	116
urea into NH_3 and CO_2	Urease−Janus platelet MMs	blood, simulated urine	50 mM of urea to propel at 4 μm/s and 200 mM urea to propel at 8 μm/s	117

Moreover, selecting the appropriate administration route for the motors needs also to be considered.[8] Recent studies indicate that distributing NPs throughout the entire circulatory system is ineffective due to numerous biological barriers, such as protein corona, fluid flow or hemorheological barrier, which hinder their proper navigation and limit their ability to reach their target locations.[10] Self-propelled NPs might not have sufficient propulsion force to overcome these limitations, however they remain invaluable within specific body cavities, such as bladder, eye cavity, gastrointestinal tract, stomach, lung or joints, revealing their potential for diseases such as cancer,[11] osteoarthritis,[12] or from illnesses that requires breaking down biofilms,[13] overcoming mucus barriers[14] or penetrating the extracellular matrix of solid tumors.[15] This review collects of the current state of MMs and NMs, focusing on their motion in viscous media guided by external or internal control; their interaction within biointerfaces, and the locations where they have been so far applied and may be interesting for optimal therapeutic effect.

2. MICRO- AND NANOMOTORS MOTION IN VISCOUS MEDIA

MMs made their first attempt at confronting viscous media in 2013.[28] In this pioneering work, magnetically guided MMs successfully navigated through viscous fluids such as silicone oil and the vitreous within the eye, both *ex vivo* and *in vivo*. Since then, the use of MMs and NMs in overcoming biological barriers has increased considerably.[29,30] Here, we will categorize the NMs explored in viscous media in different propulsion mechanisms, specifically focusing on external stimuli and internal self-propulsion mechanisms. Tables 1 and 2 summarize the applications and associated limitations of motors based on the type of propulsion mechanism and biological media used.

2.1. Externally Actuated Micro- and Nanomotors.

Externally driven MMs and NMs are particles that are actuated by external forces such as magnetic or electric fields, light, or acoustic waves. Recently, several studies have addressed their motion in viscous environments, providing new applications in delivery, among others.[31] In this section, we discuss the challenges and opportunities associated with implementing externally controlled motors. Figure 2 depicts some examples of MMs and NMs moving by external actuators.

2.1.1. Magnetic-Actuated Micro- and Nanomotors. Magnetic particles are among the most widely used types of externally actuated MMs and NMs. Their motion is based on the use of an external magnetic field that offers controlled guidance. For instance, rotating magnetic fields can be applied to drive these motors, where the magnetic vector rotates at a fixed frequency in space, inducing a torque in the magnetic structures. Based on this effect, Fischer et al. developed screw-like NMs based on a silica head with magnetic tails, guidable via an external magnet.[32] These nanopropellers exhibited mobility in various viscous environments, including Newtonian (e.g., glycerol), and non-Newtonian fluids (such as hyaluronic acid, with complex rheological properties), found in biological tissues, improving their results toward the microscale motors counterparts.[17] Almost simultaneously, Nelson et al. reported the large-scale production of artificial bacterial flagella MMs that can swim using weak magnetic fields.[33] These controllable

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Table 2. Summary of Different Propulsion Mechanisms, Their Applications, and Their Associated Limitations

propulsion mechanisms	applications	limitations	refs
magnetic propulsion	targeted drug delivery	requires external fields	17, 34−52
	motion easily guided *in vivo*	limited penetration in dense tissues	
	theragnostic	possible heating effects	
acoustic-powered	deep tissue drug delivery	requires external ultrasound source	53−72
	theragnostic	potential tissue heating	
	blood clot disruption		
light-propelled	controlled drug release	requires external light source	4, 43, 73−91
	photothermal therapy	limited tissue penetration	
	biosensing	potential phototoxicity	
powered by catalyst and chemical reactions	drug delivery	limited biocompatibility	2, 92−105
	sensing	toxicity of fuels (e.g., hydrogen peroxide)	
		controlled and directional motion	
powered by biocatalysis	targeted drug delivery	substrate availability *in vivo*	106−117
	biosensing	potential immune responses	
		variability in enzyme activity	
		controlled and directional motion	

MMs demonstrated precise navigation, capable of moving forward and backward, achieving velocities of 1.2 μm/s. Furthermore, they also exhibited the ability to translate and rotate microspheres, showcasing its potential for precise manipulation tasks in fluid environments.

In other types of applications, MMs and NMs have been used to investigate the rheological properties of extracellular environments. In that regard, Ghosh et al. correlated the motion of magnetic MMs with the rheology of blood, serving as a rheological sensor *in situ*. Faster motion corresponded to lower viscosity of the blood.[34] By measuring the deformability of red blood cell membranes, which can become less stiff in some diseases, the MMs demonstrated their potential as valuable tools for diagnosis, emphasizing their applicability in studying rheological properties that are relevant to medical practice.

Regarding for the therapeutic use of magnetic MMs, hybrid systems incorporating cells, such as sperm cells, have demonstrated targeted cargo delivery in diverse environments. Schmidt et al. employed the locomotive ability of sperm cells to propel biohybrid micropropellers, named spermbots,[35] that were magnetized to guide their motion by external magnetic fields.[36] They found these MMs successfully navigated through complex fluids like bovine oviduct fluid, as well as viscoelastic mimic fluids modeled with sperm medium.[37]

Whereas one individual motor does not pose biomedical interest, the concept of a swarm, which refers to the collective motion of thousands of motors, is currently gaining considerable attention. To understand their fundamental aspects, Zhang et al. have made significant advances in enhancing the autonomous navigation of swarms of magnetic MMs and NMs.[38] They proposed a framework that uses deep learning tools for real-time autonomous distribution planning, incorporating different levels of autonomy, which range from manual navigation (no autonomy) to automated swarm control as well as fully autonomous trajectory tracking and target reaching. This enabled the MMs to learn optimal distributions or morphologies that can be adapted as a function of the environment. They also presented in another study a bimodal actuation strategy for artificial colloidal systems, combining dual-responsive magnetic and optical fields.[39] This approach enables the 3D manipulation of self-assembled colloidal collectives, allowing the creation of more sophisticated structures by using these collectives as building blocks and even achieving structures that are not thermodynamically stable through the application of an external magnet. The authors also showed that dual-responsive colloidal collectives can serve as MMs collectives with excellent environmental adaptability for controlled 3D motions in biofluids with high viscosity and high ionic concentration. These studies mainly aim to enhance the autonomy, adaptability, and control of MMs swarms for applications like targeted delivery, progressing toward the development of intelligent magnetic motors swarms capable of autonomous decision-making and environmental adaptation.[40]

The significant progress made in the field of magnetic MMs and NMs swarms is bringing potential applications in biomedicine, such as tools for medical imaging modalities (fluorescence microscopy,[41−43] photoacoustic,[44] ultrasound,[45] and magnetic resonance imaging,[46] targeted drug,[47,48] or cell delivery,[49] thrombus ablation,[50] and biofilm eradication.[51,52]

2.1.2. Acoustic-Actuated Micro- and Nanomotors. Ultrasound-powered MMs and NMs, guided by acoustic waves, hold significant promise for a wide range of biomedical applications.[53] These nanosystems can move and navigate on the command of acoustic forces. Their advantages include fuel-free navigation, a simple configuration, low cost, and high biocompatibility. Their speed can be controlled precisely by adjusting the amplitude of the acoustic field, enabling dynamic responses.[54] Most notably, their ability to penetrate deeply into biological tissues makes them particularly advantageous for advancing biomedical research.[54−56] They exhibit enhanced capabilities when integrated with other external propulsion mechanisms. For instance, the power and precision of ultrasounds, coupled with the guidance provided by magnetic,[57−60] light[61] or catalytic[62] results in a synergistic improvement in both speed and directionality.

The propulsion of acoustically powered system has demonstrated notable capabilities for overcoming biological barriers, such as complex biological fluids[63] or cell membranes.[64,65] For example, the rapid internalization of nanowire motors into cells offers distinct advantages for delivery and biosensing within the intracellular space.[64,65] Their use can be extended to micro- and nanosurgery for precise tissue manipulation in minimally invasive procedures,[56,66] and cell manipulation.[67]

As previously described for magnetically based motors, the limited functionality of a single unit can be increased through the active control of a large swarm. Wang et al. made use of acoustic fields to assemble and control the behavior of catalytic Pt−Au nanowire motors. They demonstrated the motors' reversible swarming, separation, and directionality, by precisely

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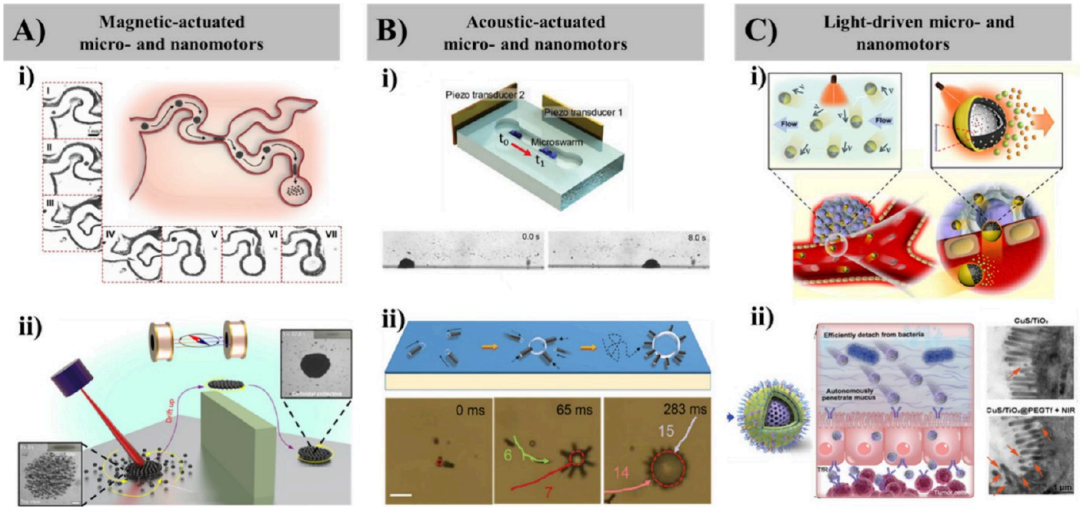

Figure 2. Examples of MMs and NMs through different propulsion mechanisms mediated by external forces. (A) Magnetic actuated MMs, showing (i) the potential applications of the different swarm configurations showing environmental adaptability.[40] Reproduced or adapted with permission from ref 40. Copyright 2021 American Chemical Society. (ii) Scheme of the self-assembled colloidal collective navigating a complex environment, mediated by the combined magnetic and optical field. The bimodal actuation allowed controlled three-dimensional movement, letting the collective overcome obstacles and adapt to varying topographies.[39] Reprinted (Adapted or Reprinted in part) with permission from ref 39. Copyright 2023 Creative Commons CC BY License. Copyright 2023 American Association for the Advancement of Science. (B) Acoustic actuated MMs. (i) Navigation of swarms of MMs in a 3D model. The swarm was pushed toward the right, sliding along the vessel wall when the transducer was activated.[72] Reprinted (Adapted or Reprinted in part) with permission from ref 72. Copyright 2022 Creative Commons CC-BY-NC License. Copyright 2022 John Wiley and Sons. (ii) Individual ultrasound-powered MMs exhibited rapid schooling forming a group of MMs, which due to the inflation of microbubbles (red dashed circle), resulted in an ultrafast growth of dandelion-like microswarms.[69] Reproduced or adapted with permission from ref 69. Copyright 2020 John Wiley and Sons. (C) Light-driven NMs. (i) The self-propulsion of near-infrared light-powered NMs improved NMs' penetration across blood vessels, enhancing their tumor-targeted drug delivery efficacy and their accumulation in the tumor region *in vivo*.[79] Reproduced or adapted with permission from ref 79. Copyright 2022 American Chemical Society. (ii) Near-infrared powered NMs improved intestinal mucus penetration, minimizing pathogenic bacterial interception in colorectal cancer.[85] Reproduced or adapted with permission from ref 85. Copyright 2023 John Wiley and Sons.

adjusting the ultrasound frequency.[68] Meanwhile, Lu et al. introduced a rapid strategy for generating dandelion-like microswarms from tubular MnO_2 shells and self-generated oxygen bubbles, achieving speeds up to 50 mm/s.[69] He et al. further advanced the field by developing reconfigurable liquid metal colloidal motors from a eutectic gallium−indium alloy. These motors can be modulated by acoustic field and UV-light, to dynamically form aggregates that mimic the growth of a dandelion.[70] Wang et al. also explored the aggregation of hybrid TiO_2−Au microbowl motors using an acoustic pressure gradient. They found that these motors move away from the center of the node when exposed to UV-light.[71] Recently, Ahmed et al. developed an acoustic-fluidic physics-based system for manipulating MMs.[72] Their system demonstrated effective control of MMs swarms in conditions that mimic human vasculature, showing precise cross- and upstream navigation against physiologically relevant flow rates of up to 16.7 cm/s, even under complex conditions such as pulsatile flow in mice. Preliminary results indicated that drug coupling does not impair swarm formation or navigation, highlighting its potential for *in vivo* applications and drug delivery.

2.1.3. Light-Driven Micro- and Nanomotors. Light-powered MMs and NMs use light as their power source for self-propulsion. They are composed of photoactive materials, and their movement can be facilitated by different mechanisms, such as photothermal reactions, which convert absorbed light into heat, or photochromic reaction, where material's optical properties change in response to light, creating an asymmetrical field of products or energy around the motors.[73] UV-light was typically used to drive the motors. However, it supposes a drawback due to the potential tissue damage in biomedical applications.[4] Therefore, other types of light sources, such as visible light,[74] or near-infrared (NIR),[75] are currently being explored. In this context, Sun et al. investigated the application of NIR-powered Janus NMs to mitigate $\alpha\beta$ protein aggregation associated with Alzheimer's disease.[76] They tethered an inhibitor peptide to the Janus-NMs. The use of NIR-light propulsion enhanced the chances of interactions between $\alpha\beta$ species and the inhibitor molecules on the NMs' surface, facilitated by collisions between them and the aggregates. As a result, the successful inhibition of $\alpha\beta$ fibrillogenesis was achieved.

Recently, light-powered NMs have shown promising potential for cancer treatment. Several studies have demonstrated the ability to target tumor cells,[77] enhance the penetration into the tumor tissue,[78] and accumulate within the tumor site.[79] Zhang et al. developed biomimetic silica NMs powered by NIR light. These NMs were used for the combined treatment of breast cancer through chemotherapy and photothermal therapy.[80] In another study, He et al. introduced a Janus mesoporous silica-based NMs (MPCM@JMSNM), coated with a macrophage membrane, which were propelled by self-thermophoresis.[81] This process was triggered by the photothermal effect of the gold half-shells upon exposure to NIR light, causing the NMs to move approximately 8 times faster than their passive controls. The macrophage membrane coating enabled these NMs to actively target tumor cells and penetrate their cell membranes, in collaboration with a self-

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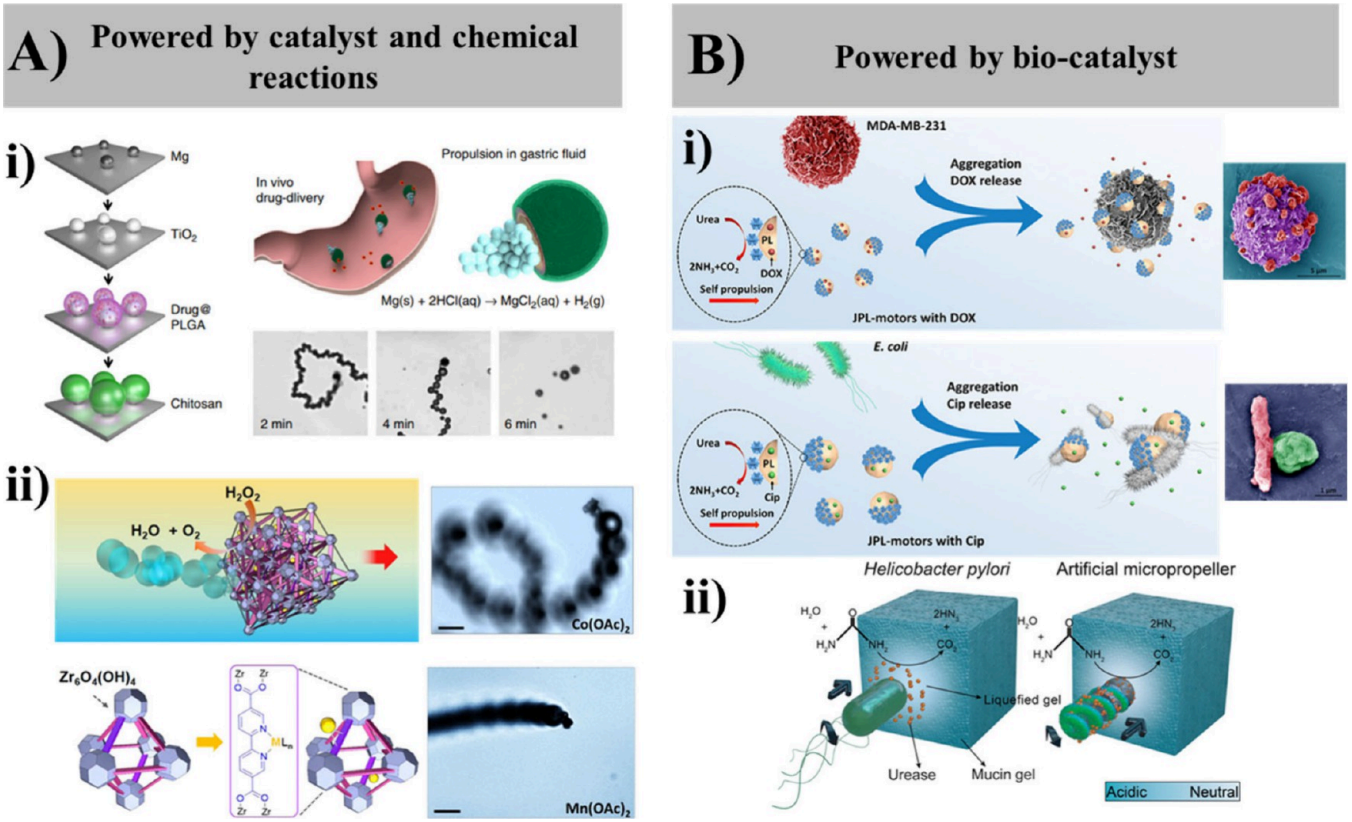

Figure 3. Examples of MMs and NMs employing different propulsion mechanisms mediated by internal chemical reactions. (A) Powered by catalysts and chemical reactions; (i) Janus MMs made of Mg, TiO_2, PLGA, and chitosan, showing propulsion mediated by Mg catalysts in simulated gastric fluid.[102] Reprinted (Adapted or Reprinted in part) with permission from ref 102. Copyright 2017 Creative Commons CC BY License. Copyright 2017 Springer Nature. (ii) MMs based on a metal−organic framework capable of decomposing H_2O_2 into H_2O and O_2 when doped with Co or Mn.[103] Reproduced or adapted with permission from ref 103. Copyright 2016 American Chemical Society. (B) Powered by biocatalysts. (i) Janus platelet MMs capable of decomposing urea into NH_3 and CO_2 to enhance motion for breast cancer and bacterium-targeted delivery applications.[117] Reproduced or adapted with permission from ref 117. Copyright 2020 American Association for the Advancement of Science. (ii) MMs that use urease to liquefy the environment and enhance motion in mucin gel in combination with active magnetic propellers.[114] Reproduced or adapted with permission from ref 114. Copyright 2015 American Association for the Advancement of Science.

electrophoretic force, *in vitro*. Furthermore, ongoing research now focuses on *in vivo* tumor penetration. Ma et al. developed NMs based on platinum and doxorubicin. The generation of oxygen from a Pt-catalyzed reaction with hydrogen peroxide (H_2O_2) improved the NMs' tissue penetration, cellular uptake, and drug delivery efficiency.[82]

Other uses of light-driven motors involve the penetration of various biological barriers, including cellular membranes,[83] and mucus.[84,85] Furthermore, their potential extends to applications in thrombolysis for clot eradication,[86] antifungal properties,[87] bacterial biofilm erradication,[88] and promoting wound healing.[89] Moreover, they have been employed in medical imaging techniques, including fluorescence imaging,[43] photoacoustic imaging,[90] and for magnetic resonance imaging.[91]

2.2. Chemically Propelled Micro- and Nanomotors. Chemically and enzyme-powered MMs and NMs have predominantly been investigated in aqueous environments, where they exhibit remarkable potential for diverse applications such as targeted drug delivery systems. However, their use in more complex and challenging environments, such as biological fluids and heterogeneous systems, remains challenging. This limited exploration can be attributed to the intricate interaction of enzymes with nonaqueous media, as well as the need for tailored motors designs that can operate effectively and efficiently under these conditions. Future research in this area holds the promise of expanding the scope of enzyme-powered motors and unlocking their potential in a broader range of applications. Some examples of MMs and NMs chemically propelled are depicted in Figure 3 and Table 1.

2.2.1. Powered by Catalyst and Chemical Reactions. For many years, nature has developed complex motors that catalyze chemical energy into mechanical work. Scientists have attempted to replicate this by developing intelligent systems, where micro- and nanoparticles can move autonomously through chemical reactions, avoiding the need for external control. A key difference lies in the control mechanism, where magnetic control operates within the magnetic particle, while concentration-based fuel works at the boundary between the particle and the fluid. This induces movement that varies, depending on the fluid's viscosity, as was reported by Mallouk, Sen et al.[2] In that sense, a platinum-based particle was synthesized, capable of decomposing H_2O_2 and using the resulting energy to self-propel at speeds of up to 30 μm/s. Tubular microjets showed also very powerful propulsion based on the thrust of oxygen bubbles originated from the same Pt−H_2O_2[92] or catalase-H_2O_2[19] superfast speeds were achieved,[93] but they motion was significantly hindered in

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blood samples[94] unless physiological temperatures were used.[95] Nanojets could drill into biomaterials coated fixed HeLa cells.[96] However, the high concentration of H_2O_2 used to propel microjets has limited their applications in biomedical applications. Wang et al. engineered the first MMs that can achieve a velocity of 3 mm/s using only water to produce hydrogen, eliminating the need for H_2O_2.[97] For that, they fabricated Janus MMs, featuring a one-sided titanium coating with a binary Al−Ga microsphere. This structure immediately ejected bubbles upon contact with water. They demonstrated MMs' ability to navigate in human viscous media, such as serum or cell culture media. However, due to the high viscosity of these media, the speed was reduced to 500 and 1200 μm/s, respectively. Related studies have indicated that Janus Ga/Zn MMs can navigate through simulated gastroenteric acid effectively, achieving a speed of 383 μm/s.[98]

Over the last years, the potential of self-propelled NPs, in the field of biomedicine, started to be acknowledged by researchers. For instance, Janus $CaCO_3$ MMs were developed as biocompatible and biodegradable asymmetric motors,[99] that moves in low acidic conditions resulting from tumor growth by degrading themselves. A similar strategy was applied by Wang, Zhang et al. by fabricating synthetic poly(3,4-ethylendioxythiophene) (PEDOT)/zinc-based MMs.[100] These acid-powered MMs are capable of self-propulsion in an *in vivo* mouse stomach following oral administration, representing the first application of chemically powered MMs in live animals. Notably, the core of the MMs can gradually degrade in the acidic gastric environment, thereby releasing its cargo. Indeed, the use of MMs for drug delivery into the stomach is rapidly gaining interest, with a growing number of advancements in the field. In 2017, the same authors introduced a Mg-based MMs, which are propelled by the production of hydrogen.[101] Furthermore, they engineered MMs with a pH-sensitive polymer coating, enabling drug release in highly acidic environments. This innovative design confers dual functionality to the gastric media, serving both as a fuel source for propulsion and a trigger for drug release. The promising results led to *in vivo* trials,[102] aimed to treating *Helicobacter pylori* (*H. pylori*) infections in a mouse model, ensuring that the drug-loaded MMs could disperse throughout the entire stomach and penetrate the tissue. Notably, these MMs demonstrated more than double the antimicrobial effect compared with passive particles, enhancing the efficacy of antimicrobial treatments.

It has been demonstrated that a variety of materials can be engineered to function as chemically powered motors. One example is metal−organic frameworks (MOFs), which are currently a subject of interest in the field of chemistry. The versatility of MOFs, constructed from metal nodes and organic linkers, opens up a wide range of applications. For instance, by incorporating a bipyridine ligand, these MOFs can be transformed into MMs.[103] This modification converts nanostructures into catalytic engines that propel the MMs using chemical fuel with propulsion controlled by the introduction of chelating agents. These agents bind to the metal ion, thereby suppressing the catalytic activity and effectively switching the propulsion on or off. The authors reported that changing the metal from Co^{2+} to Mn^{2+} increased the speed of the MMs from 40 μm/s to 60 μm/s at a fuel concentration of 15%, probing the versatility and potential of these MMs.

Chemically self-propelled motors have also been developed on the nanoscale to improve their biomedical applications. For instance, Janus NMs composed of iron oxide and polydopamine have been engineered to navigate within biofilms.[104] These NMs demonstrated antimicrobial properties, reducing colony formation in *in vivo* animal models of burn wounds. The NMs' movement is facilitated by nitric oxide (NO), produced due to elevated levels of glutathione within the biofilms. Comparable strategies have employed biodegradable hybrid NMs powered by catalytic inorganic MnO_2. These NMs can achieve a speed of 15 μm/s in the presence of just 5 mM of H_2O_2, enhancing penetration capabilities into 3D cell spheroids.[105]

In summary, the evolution of self-propelled MMs and NMs, powered by chemical fuels and featuring diverse control mechanisms and materials, reveals their expanding role in biomedicine, encompassing drug delivery, antimicrobial efficacy, and versatile applications in human biological environments.

2.2.2. Powered by Biocatalyst. Pathogenic entities in nature, such as bacteria, have evolved enzymes with the ability to degrade biological barriers, facilitating tissue penetration and systemic infection. One illustrative example is bacteria *Helicobacter pylori*, which employs urease to elevate the pH of mucosal secretions, inducing liquefaction for enhanced motility.[106] Inspired by these natural mechanisms, researchers have replicated this phenomenon by immobilizing enzymes on the surface of NPs. These engineered NPs demonstrate self-propulsion, driven by the chemical products produced through enzymatic activity. A pioneering approach has demonstrated that enzymes, such as catalase, urease, and glucose oxidase, can be utilized to propel silica motors.[107] Subsequently, it was shown that these NMs can serve as effective carriers, enhancing drug release by simultaneously increasing the fuel concentration.[108] In fundamental studies, Sen et al. conducted an in-depth study into the underlying mechanisms of chemotactic behavior.[109] They revealed that liposomes coated with catalase exhibited positive chemotaxis by moving toward the fuel source, while those coated with urease demonstrated negative chemotaxis by moving away from it. These findings reinforce the evidence that particles can guide their directionality based on the products formed during enzymatic reactions. Furthermore, the influence of specific salts on chemotaxis can be further understood through the Hofmeister series, which classifies ions based on their ability to stabilize or destabilize macromolecular structures, suggesting that motion might also be influenced by the presence of salts, as it could facilitate ion transfer.[110] Nevertheless, the efficiency of motion can be significantly amplified through various strategies. For instance, constructing a multilayered enzyme structure on the surface of MMs has been show to increase their speed by up to five times compared to those with a monolayer enzyme structure.[111] Additionally, purifying the as-received urease used in the fabrication of MMs has resulted in motion speeds reaching up to 5.5 μm/s, 2.5 times higher than those of unpurified enzyme. This purification process also improved their reusability, compared to their nonpurified counterparts.[112]

Moreover, the current trend is shifting toward the development of more biocompatible and biodegradable motors, which may be more suitable for biomedical applications. For instance, poly lactic-*co*-glycolic acid (PLGA) NPs appear to be a promising approach to fabricate NMs, as they have already demonstrated propulsion just by using 1 mM of H_2O_2 fuel at the single particle level.[113]

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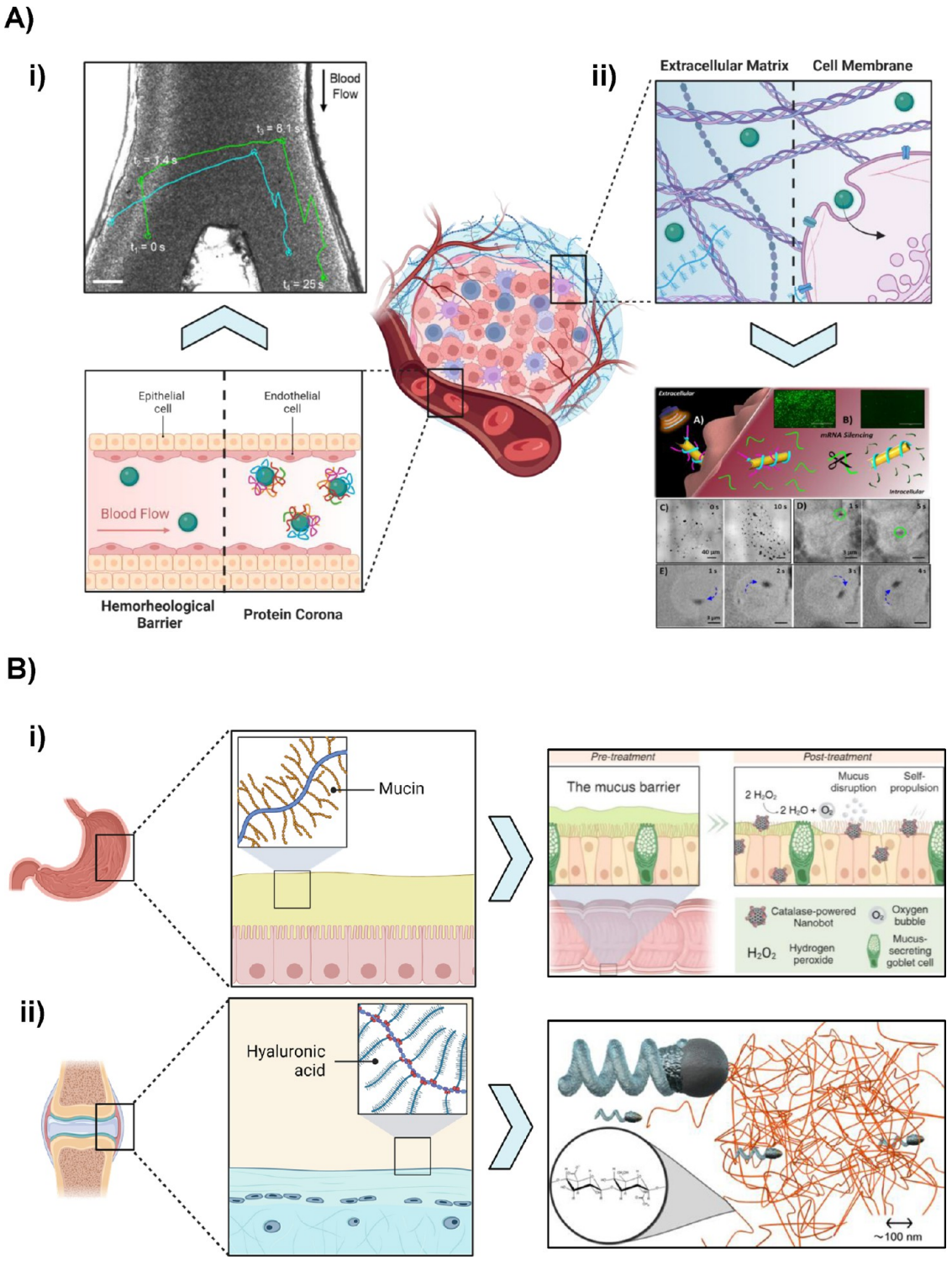

Figure 4. Navigating through complex environments. Different types of biological barriers are encountered in nanomedicine, emphasizing the challenges posed by varying levels of biological structures: (a) Intravascular barriers. (i) Hemorheological barrier or protein corona.[119] Reproduced or adapted with permission from ref 119. Copyright 2020 The American Association for the Advancement of Science. (ii) Extracellular matrix.[65] Reproduced or adapted with permission from ref 65. Copyright 2016 American Chemical Society. (b) Barriers composed of viscous media. (i) Mucin.[14] Reproduced or adapted with permission from ref 14. Copyright 2024 American Chemical Society. (ii) Hyaluronic.[32] Reproduced or adapted with permission from ref 32. Copyright 2014 American Chemical Society.

All of the fundamental understanding gained from enzymatically propelled motors has been utilized in recent years to develop MMs and NMs capable of navigating through highly viscous media, thereby overcoming biological barriers. In a study conducted by Fischer et al. in 2015, urease was anchored to nanopropellers to facilitate penetration into mucin gels.[114] They observed a motion of 1.25 μm/s for the motors in the presence of a 2−5 wt % viscous mucin solution with urea. Furthermore, Städler et al. demonstrated that MMs, capable of moving within 3D collagen gel spheroids under external

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magnetic control, exhibited enhanced mobility. This enhancement was observed when collagenase enzymes, known for their ability to break down collagen fibers, were attached to the surfaces of the MMs. Remarkably, they observed up to a 15-fold enhancement in mobility with just 1 mM of Ca^{2+}.[115] A similar study found that the size of polystyrene-based MMs (1−4 μm) impacts their interaction with collagen gels.[107] Larger NMs were entrapped in the collagen's pore mesh, hindering their motion. Optimal velocities of 10−12 μm/s were achieved on fiber networks with larger pores, while denser networks necessitated smaller particles for comparable velocities.

With the introduction of NMs capable of navigating through viscous media, a plethora of innovative approaches has been developed. For instance, tadpole-like brushes, based on block copolymers and measuring less than 100 nm, have been synthesized through radical polymerization.[116] These brushes have catalase enzymes attached to their surfaces, enabling the NMs to move within a viscous tumor environment. Remarkably, this motion is facilitated using just 2 mM of H_2O_2, achieving speeds of 15 μm/s, which can increase up to 24 μm/s with 10 mM of H_2O_2. In a different approach, urease was asymmetrically immobilized on Janus platelet MMs to augment their diffusion in blood and simulated urine.[117] The authors observed notable enhancements in motion starting at a urea concentration of 50 mM, where the byproducts of ammonia and carbon dioxide propelled the particles. A speed of 4 μm/s was reported, which increased to approximately 8 μm/s when the urea concentration was elevated to 200 mM.

In summary, enzymatically propelled MMs and NMs, inspired by entities from nature, have shown potential for navigating complex biological barriers. Some of their specific *in vivo* demonstrations are described in the following sections. Recent advancements in moving through viscous media highlight diverse strategies for overcoming biological barriers, paving the way for targeted drug delivery, and pointing up the potential of these nanosystems in biomedical applications.

3. MICRO- AND NANOMOTORS INTERACTING WITH BIOLOGICAL BARRIERS

Biological barriers act as defense mechanisms in our body to protect us against potential harm, including pathogens and foreign substances.[118] These mechanisms are essential for preserving the overall health. They are diverse in composition, including intravascular, endothelial, and cellular barriers as well as highly viscous environments. However, they pose a significant challenge in the application of NPs in biomedical applications since passive NPs often become trapped in complex structures, reducing their ability to reach the desired destination effectively. MMs and NMs have emerged as a promising strategy to facilitate interactions with and the modulation of biological barriers. Their primary strategy lies in improving the efficiency of reaching specific targets, thereby optimizing drug delivery and prolonging their half-life time.

The hemorheological barrier is based on the complex dynamics of blood flow and the interactions of NPs with proteins (protein corona effect; Figure 4a(i)). In this sense, magnetic MMs have performed upstream movement *in vitro*[119] and *ex vivo*[120] models within the blood flow. Moreover, protein corona can be reduced by shielding the NP surface with hydrophilic polymers, such as polyethylene glycol (PEG).[121] However, this approach may face some obstacles due to the accelerated blood clearance phenomenon, which involves the rapid elimination of PEGylated nanocarriers from circulation.[9,122,123] Also, enzyme-powered NMs, developed by Sánchez et al., showed a 20% reduction in protein corona effect compared with passive NPs. Interestingly, even in the presence of this common process for NPs, the materials demonstrated enhanced diffusion, indicating that their movement remained unhindered.[124] Recently, other innovative strategies have gained attention preventing the absorption of protein corona and avoiding the immune system's recognition by grafting their surface with cell membranes.[125]

Furthermore, to reach the target site, it is necessary not only to navigate through the viscous extracellular matrix but also to penetrate the cell for effective drug uptake (Figure 4a(ii)). In this regard, another obstacle is the barrier presented by the cell membrane. To overcome this challenge and enhance intracellular delivery several approaches have been explored including the functionalization of cell-penetrating peptides[126] or the incorporation of different ligands.[127] Moreover, various strategies such as ultrasound-guided NMs,[128] magnetically guided,[129] chemically driven,[130] and enzyme-powered NMs[131] have demonstrated the ability to transverse cell membranes and enhance uptake.

In viscous environments, fluids are densely populated with biomolecules, including cell media, hyaluronic acid, and collagen fibers, which contribute to their high viscosity. Many MMs and NMs have been reported to exhibit motion under these conditions, such as vitreous humor,[132,133] hyaluronic acid,[134,135] collagen,[107,115,131] or mucus[136,137] (Figure 4b).

In summary, MMs and NMs offer a promising solution to surpass biological barriers, providing numerous advantages. Their motion, navigation, cargo transport, and biocompatibility in biological environments enhance their application in biomedical therapies and diagnostics. The prospect of this innovation has the potential to initiate a new era of enhanced healthcare outcomes.

4. CHARACTERIZING NANOMATERIALS−BIOINTERFACE INTERACTIONS

In recent years, scientists have made significant advancements in the development of smart materials to address the challenges posed by the different biological barriers in the human body, as cited in the previously section. In particular, surface grafting of these materials has demonstrated the ability to fine-tune interactions with various biological barriers, such as stomach mucus, ocular mucus, and proteins, among others.[138] For instance, this modulation aims to enhance mucus adhesion and penetration, while reducing the undesirable protein corona effect. In this sense, several strategies have been developed to utilize biocompatible and biodegradable polymers that interact with biological barriers to produce dual effects. One such strategy involves the use of Eudragits, a well-known FDA-approved polymer commonly used in pharmacy. Recently, Eudragits have been combined with other mucoadhesive polymers to enhance the adhesion of hydrogels to the ocular mucosal layer.[139] The effectiveness of this adhesion was quantified by using rheology. In these experiments, an *ex vivo* conjunctiva containing mucus was attached to one plate of a rheometer, while the materials were anchored to another. The force required by the instrument to detach both disks was then mathematically converted to measure the mucoadhesivity of the materials. In addition, other polymers, such as pH-responsive polyanions, were employed to cross the phospho-

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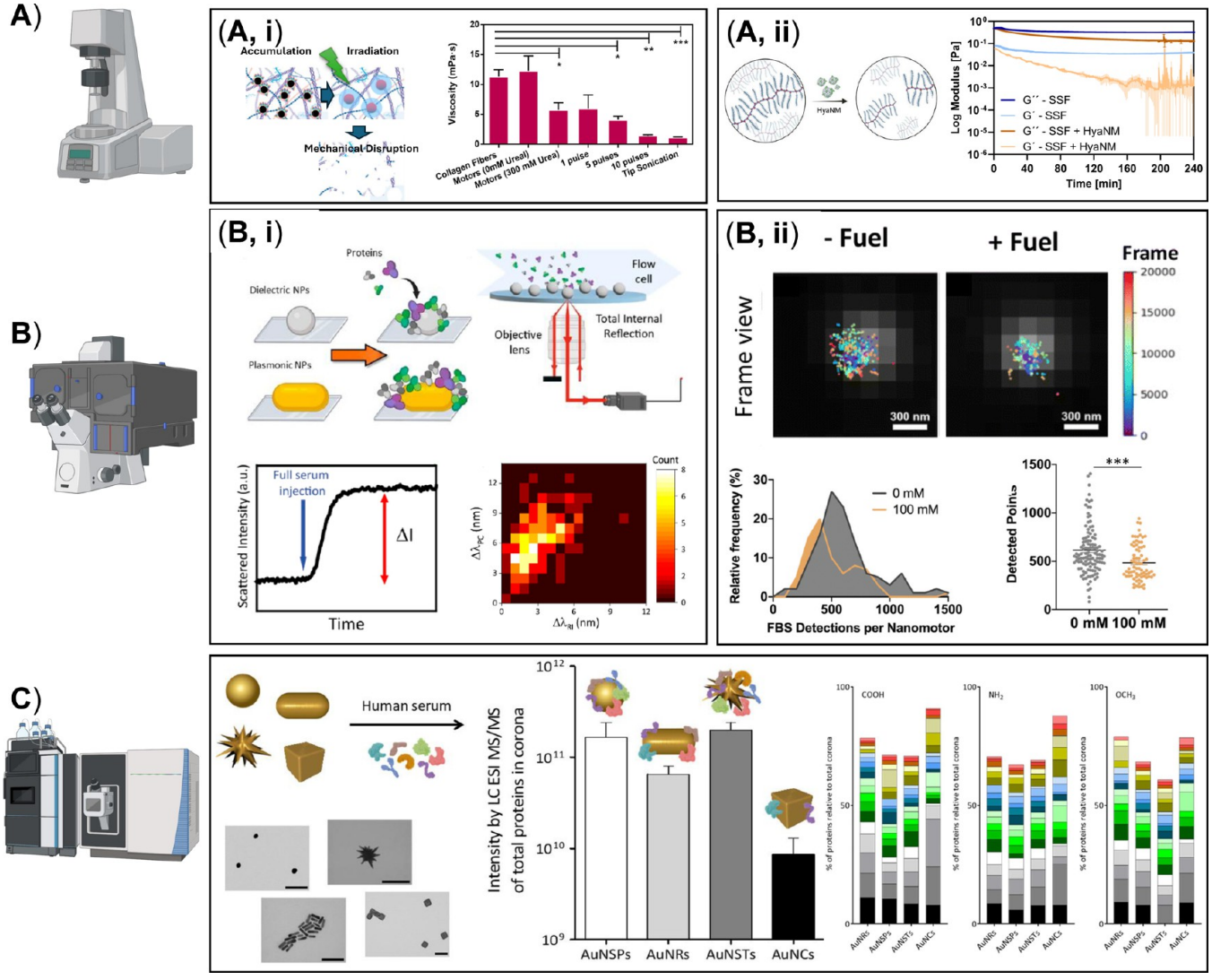

Figure 5. Techniques used for the quantification of nanomaterials' biointerfaces. (A) Rheometer for monitoring the disruption of (A, (i)) collagen fibers through light-induced actions that reduce viscosity.[131] Reprinted (Adapted or Reprinted in part) with permission from ref 131. Copyright 2023 Creative Commons CC BY License. Copyright 2019 Springer Nature. (A, (ii)) Synthetic synovial fluid by diminishing viscoelastic properties via the activity of hyaluronidase-based silica NMs.[134] Reprinted (Adapted or Reprinted in part) with permission from ref 134. Copyright 2024 Creative Commons CC-BY-NC License. Copyright 2024 John Wiley and Sons. (B) Optical microscope for quantifying protein corona absorption on (B, (i)) gold nanorods, using internal reflection excitation for single-particle scattering microscopy, showing an increase in scattering cross-section due to the local refractive index rise from protein corona formation.[143] Reproduced or adapted with permission from ref 143. Copyright 2023 American Chemical Society. (B, (ii)) Mesoporous-based enzymatic NMs, analyzed with Stochastic Optical Resolution Microscopy in the presence and absence of fuel, accompanied by a histogram of FBS detection per NM distribution.[124] Reproduced with permission from ref 124. Copyright 2023 Royal Society of Chemistry. (C) Liquid chromatography-electrospray ionization-tandem mass spectrometry for quantifying protein absorption on gold nanoparticles, as a function of their shape and ligand.[144] Reproduced or adapted with permission from ref 144. Copyright 2020 Elsevier.

lipid membranes of mammalian cell.[140] This capability stems from their distinctive colloid-to-globule transition, triggered by a shift in pH from 7 to 4. All of the aforementioned strategies have also been applied to MMs and NMs. For instance, hydrophilic coatings comprising PEG, polyvinylpyrrolidone (PVP), or hyaluronic acid were strategically applied around silica NMs to mitigate their interactions with viscous environments.[141] This coating approach aimed to enhance the mobility of the NPs within *ex vivo* porcine vitreous and collagen gel. The results showed that the incorporation of enzymes, such as collagenase and hyaluronidase, onto the material surfaces significantly improved particle motion. This enhancement was attributed to the enzymatic degradation of the viscous matrices, which led to a substantial reduction in viscosity and, consequently, an increase in particle mobility. Recent studies have applied these concepts to NMs capable of mechanically disrupting collagen fibers via laser pulses. These NMs were characterized by monitoring the decrease in collagen viscosity following specific durations of laser irradiation (Figure 5A,(i)).[131] In another study, it was shown that NMs, when anchored with hyaluronidase on their surface, can effectively reduce and regulate the viscosity of *ex vivo* synovial fluid (SF) from joints (Figure 5A,(ii)).[134] The authors examined the loss and storage moduli, which are indicative of the solid and liquid behavior of the viscous biological media, of the SF in the presence of a certain quantity of NMs over time.

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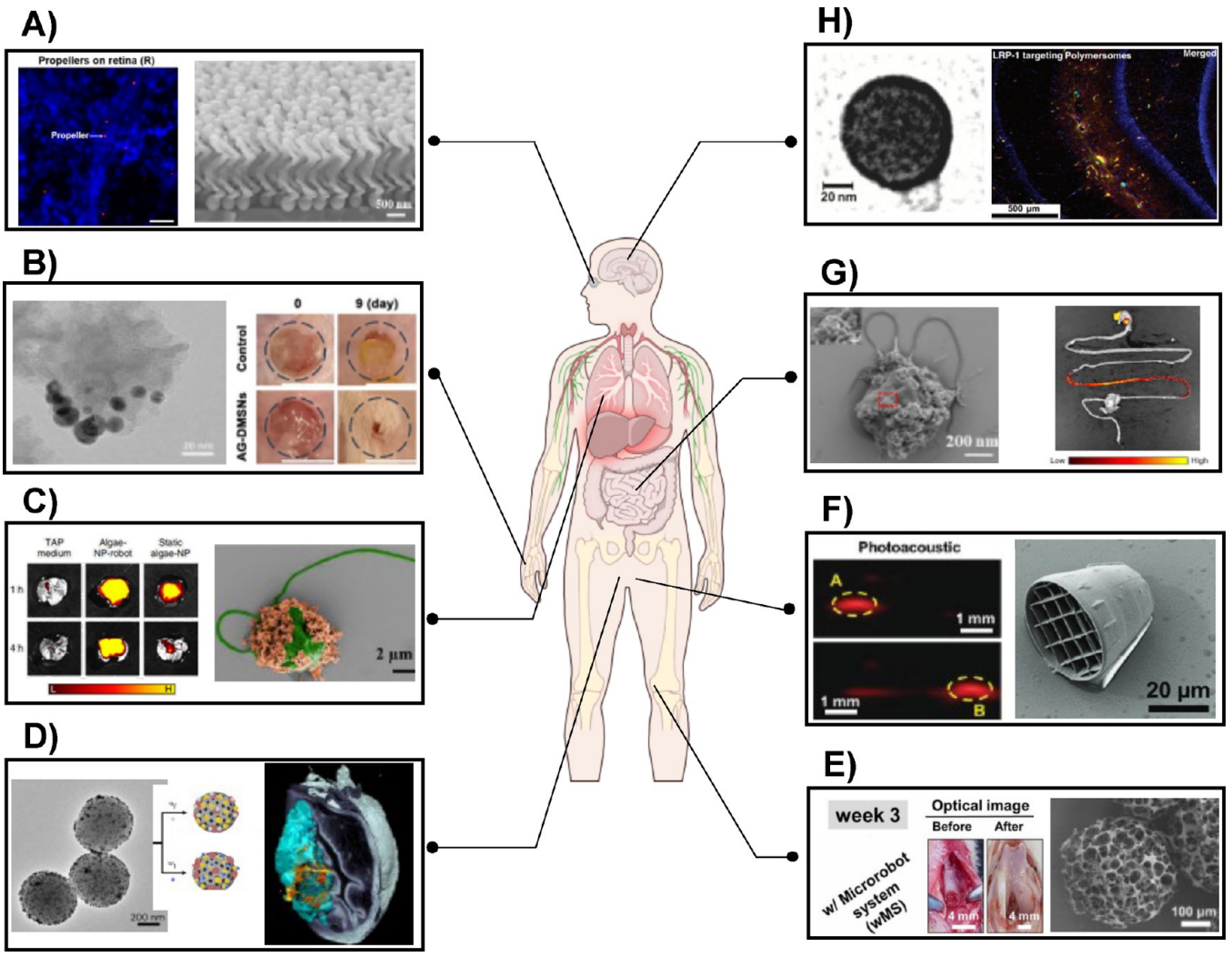

Figure 6. Examples of different types of MMs and NMs in various *in vivo* locations. (a) In the eye, helical magnetic micropropellers (in red) penetrated the complex vitreous network and propelled toward the retina (cell nuclei stained in blue).[132] Reprinted (Adapted or Reprinted in part) with permission from ref 132. Copyright 2018 Creative Commons CC-BY-NC License. Copyright 2018 American Association for the Advancement of Science. (b) In the skin, platinum-based NMs demonstrated enhanced skin penetration and transdermal drug delivery for synergistic antifungal therapy, resulting in complete wound healing and scab reduction.[151] Reproduced or adapted with permission from ref 151. Copyright 2021 American Chemical Society. (c) In the lung, algae-based NMs were used to treat lung bacterial infections, and their distribution was examined postintratracheal administration via fluorescence imaging.[164] Reproduced or adapted with permission from ref 164. Copyright 2022 Springer Nature. (d) In the bladder, silica-based NMs demonstrated tumor accumulation and reduction in mouse bladders using a single administration.[11] Reprinted (Adapted or Reprinted in part) with permission from ref 11. Copyright 2024 Creative Commons CC BY License. Copyright 2024 Springer Nature. (e) In the knee, human adipose-derived MMs were employed for targeted cell delivery in cartilage regeneration, enhancing the delivery of mesenchymal cells as visualized by optical microscopy.[179] Reproduced or adapted with permission from ref 179. Copyright 2020 The American Association for the Advancement of Science. (f) In the urogenital tract, polymersome-based MMs demonstrated efficient actuation as a swarm of sperm microcarriers, tracked using a photoacoustic imaging system.[186] Reprinted (Adapted or Reprinted in part) with permission from ref 186. Copyright 2022 Creative Commons CC-BY-NC License. Copyright 2022 John Wiley and Sons. (g) In the gastrointestinal tract, algae-based MMs showed efficient motion and extended lifetime when encapsulated in a protective oral capsule, enhancing cargo delivery in the tract.[192] Reproduced or adapted with permission from ref 192. Copyright 2022 The American Association for the Advancement of Science. (h) In the brain, asymmetric polymersome NMs showed chemotactic behavior and targeted the blood-brain barrier, increasing brain penetration compared to passive NPs.[23] Reprinted (Adapted or Reprinted in part) with permission from ref 23. Copyright 2017 Creative Commons CC BY License. Copyright 2017 The American Association for the Advancement of Science.

They observed a reduction in the viscoelastic properties of SF, which facilitated faster propulsion of the NMs in the medium. Similarly, oscillatory magnetic microrheology was employed to characterize enzyme-based NMs within spherical probes in *ex vivo* porcine vitreous, synthesized collagen gel, and hyaluronic gel.[141] The enzymes collagenase and hyaluronidase were attached to the surface of the MMs, demonstrating enhanced motion by altering the rheology of the viscous media.

Another undesired phenomenon that occurs at the biointerface of nanomaterials is the so-called "protein corona" effect.[142] Depending on the adhesion forces, this effect can be categorized into a "soft" or "hard" protein corona. The reversibility of this effect may be compromised depending on

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the strength of these forces. Recently, a variety of techniques have been employed to measure the amount of protein adhering to a given material *in vitro*. In discussing potential *in vivo* applications of similar strategies, it is worth noting that corona formation in a living system could differ significantly. One such technique, real-time all-optical NPs analysis via scattering microscopy, has been used to monitor the formation of protein coronas in full serum at the individual particle level, eliminating the need for label molecules for metallic and dielectric NPs (Figure 5B,(i)).[143] This method revealed multiphase behavior on porous NPs, involving an initial fast adsorption phase followed by slower protein migration into the porous structures, as confirmed by the authors using super-resolution microscopy. Moreover, the technique demonstrated significant heterogeneity in protein corona formation on NPs with protein masses varying by more than an order of magnitude in undiluted blood serum. In the context of NMs interactions, a recent study employed fluorescently labeled serum proteins to quantify the protein corona on mesoporous NMs, through super resolution microscopy (Figure 5B,(ii)).[124] The authors concluded that when the NMs are active, the protein corona effect is diminished. This finding reveals the advantages of active NMs over passive NPs, highlighting yet again the benefits of NMs. Moreover, liquid chromatography-electrospray ionization-tandem mass spectrometry was used to determine the amount of adhered protein onto gold NPs stabilized with different functional group ligands (Figure 5C).[144] This variation was also influenced by the morphology of the NPs. Specifically, the researchers reported that gold nanocages absorbed fewer proteins compared with spheres, rods, and stars. This was attributed to the nanocages' smaller surface area and pronounced surface curvature at the edges. The technique used for the protein quantification involves first separating proteins based on their physicochemical properties and then by their mass-to-charge ratio. This approach provides a comprehensive analysis of the protein corona composition on various NPs' morphologies.

In conclusion, recent advancements in the development of smart materials have demonstrated the potential for surface grafting to fine-tune interactions with biological barriers, addressing challenges within the human body. Additionally, novel techniques like rheology and NPs analysis have played key roles in characterizing and enhancing our understanding of nanomaterials' behavior, particularly in mitigating the protein corona effect. These findings contribute to the refinement of material design for biomedical applications and remark on the advantages of active nanomaterials over passive NPs, emphasizing the broader benefits of NMs in biomedical research and applications.

5. HOW TO REACH THEIR TARGET: DIRECT ADMINISTRATION OR IN PILLS

While the use of MMs and NMs offers a range of advantages described in previous sections, their application *in vivo* faces inherent challenges and limitations associated with intravenous administration.[145] First, the immune system can recognize them as foreign entities, leading to rapid clearance by the mononuclear phagocytic system, which limits their circulation time and reduces their effectiveness. Furthermore, MMs and NMs face physiological barriers, such as blood, where proteins present create a "protein corona" on the MMs and NMs. Once these barriers are surpassed, motors need to overcome dense extracellular matrices, especially in targeted tissues like tumors. These obstacles make it difficult for MMs and NMs to reach their intended destinations. Furthermore, achieving controlled propulsion and navigation in the bloodstream and other complex environments is challenging, which can reduce their effectiveness in drug delivery applications. One proposed solution has been the direct administration of motors to the specific target site. A simplified classification was established based on the accessibility of each organ for medical interventions. This led us to distinguish two separate groups. The first group includes organs, such as the eye, skin, bladder, lung, urogenital tract, and joints, which are directly accessible. The second group comprises locations such as stomach and brain, which are indirectly accessible.

5.1. Organs Directly Accessible.

5.1.1. The Eye. The eye, a sensitive and complex organ, poses distinct challenges for medical interventions. The potential of motors to deliver therapeutics with precision could open a new era in the treatment of ocular diseases. For that, these MMs and NMs must navigate through the vitreous humor, a gel-like substance composed of water, collagen fibers, hyaluronic acid, and various proteins.

Ullrich et al. were among the first to demonstrate real-time tracking of magnetically guided MMs in eyes.[28] For ocular diseases, Chatzipirpiridis et al. reported implantable MMs for wireless ophthalmologic surgery. These MMs, propelled by magnetic field, could be intravitreally injected into the eye of a living rabbit, demonstrating both rotational and translational movements.[146] Similarly, Wu et al. explored the ability of helical magnetic micropropellers to traverse the biopolymeric network and cover centimeter-scale distances within the *ex vivo* porcine vitreous body of the eye (Figure 6a).[132] They demonstrated that these MMs, functionalized with a perfluorocarbon surface to minimize their interactions with biopolymers, such as collagen, could navigate significant distances more precisely than passive counterparts, increasing their diffusion coefficient up to 6-fold times faster than uncoated particles.

The use of MMs in viscous media presents a challenge due to the dense gel-like networks of polymeric chains, with mesh sizes at the nanoscale. In these environments, the motion of MMs larger than the mesh size is impeded, whereas smaller NMs with diameters close to the mesh size can pass through the network with minimal resistance. Adopting this approach and scaling down to the nanoscale, Zhang et al. demonstrated the collective movement of NMs (100 nm) in bovine vitreous humor (mesh size of ca. 550 nm) and within the bovine eyeball, both experiments conducted in *ex vivo* animal samples.[133] Hence, NMs, with their controllable operations, along with their capacity to deliver therapeutics at a specific target, could provide solutions for minimally invasive surgery strategies in ophthalmologic diseases.

The use of motors in ocular applications shows promising benefits, including enhanced drug delivery to the eye's posterior segments, where therapeutic agents typically fail to reach due to physical barriers. Loading these drugs into motors could potentially improve treatments for retinal diseases. As this application is relatively new for motors, it will still require many formulation upgrades before reaching clinical trials. Incorporating mucoadhesive polymers, for instance, can ensure good ocular attachment to the retina, while mucopenetrating polymers will allow the motors to cross faster, overcoming ocular barriers. Passive NPs[147] have already shown promising results in this field, and it is likely that NMs will stand out due

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to their superior capabilities, as they are less likely to become trapped in complex media, thus speeding up the path to clinical translation.

5.1.2. The Skin. As the body's largest organ, the skin serves as the primary barrier against external pathogens that treatments must to overcome.[148] Despite its protective role, the skin remains vulnerable to various infections, particularly those caused by biofilms, which shield bacteria from antibiotics and the immune system.[149] Nanotechnology has introduced the use of NMs, self-propelled by light,[150−154] or biohybrid[155,156] to combat bacterial infections. These NMs can infiltrate biofilms and deliver targeted treatment, thereby enhancing the effectiveness of conventional therapies. Enzyme-powered NMs have shown considerable promise in recent studies. For instance, urease-powered NMs have effectively reduced bacterial biofilms by 60% *in vitro*, leveraging the enzymatic products of urease to enhance their bactericidal activity.[157] Their efficacy was further validated *in vivo* when combined with an antimicrobial peptide (AMPs).[158] Unlike AMPs in solution, which exhibit limited antimicrobial efficacy beyond the administration site, AMP-modified NMs not only demonstrate autonomous propulsion but also achieve up to a three-order-of-magnitude reduction in bacterial infections.

Chemically powered NMs, especially those propelled by nitric oxide (NO), have been extensively employed due to NO's bactericidal properties. For instance, Li et al. developed NO-propelled NMs that release NO in response to glutathione, demonstrating effective *in vivo* healing.[104,159] Additionally, the authors claimed that NO-driven NMs can specifically respond to H_2O_2 concentrations present in biofilms, generating reactive oxygen species (ROS) under an ultrasonic vibration. This leads to a synergistic antibacterial effect and a 98.8% antibiofilm efficiency, significantly accelerating the healing of infected muscles *in vivo*.[160] Furthermore, Liu et al. demonstrated enhanced penetration with NO-driven NMs using a catalytical cascade (Figure 6b),[161] that was later adapted to promote diabetic wound healing in infected mice by changing the substrates.[162]

The development of NMs capable of penetrating biofilms offers promising solutions for combating bacterial infections and enhancing wound healing. However, the application of NMs to the skin presents several challenges. Treating large areas can be impractical and costly compared with traditional creams and other treatments. Additionally, while NPs are already used in medicine, their use in cosmetics requires careful consideration of safety and efficacy.[148] Despite these challenges, NMs hold significant potential for localized infections and wound care, offering a solution for situations where conventional treatments might be less effective. Continued research in this area promises to further advance infection control and improve clinical outcomes.

NMs demonstrate strong clinical potential in skin applications, particularly for the targeted delivery of active ingredients and penetration into specific skin layers. Despite the challenges related to long-term safety and regulatory compliance for novel nanomaterials, their use is promising. Some nanomaterials are already incorporated into dermatological and cosmetic products, increasing the probability of the clinical adoption of motors for skin applications.

5.1.3. The Lung. Effectively delivering drug-loaded NPs into the lungs remains challenging due to instability in the formulation, originated from particle−particle interaction which often leads to aggregation, and poor delivery efficiency caused by exhalation.[163] MMs offer great potential for improving the treatment efficacy of lung diseases. Their small size and customizable surface properties enable them to navigate through complex pulmonary environments, overcoming barriers like mucus. They can be engineered for sustained drug release and precise targeting of specific lung tissues. Furthermore, by integrating biological components to create biohybrid MMs, they can offer extended operation, improved localization, and controlled delivery, thereby enhancing the efficacy of targeted delivery. For instance, algae-based biohybrid robot demonstrated successful *in vivo* treatment of *Pseudomonas aeruginosa* infection in the lung, offering significant therapeutic efficacy by reducing bacteria burden and improving animal mortality (Figure 6c).[164] Such efficient elimination of bacteria-causing pneumonia in the lungs reflects the autonomous long-lasting motion of the ciprofloxacin-loaded algae MMs in the lung fluid, which promotes robust lung distribution and prolonged retention time and enables them to evade phagocytosis by alveolar macrophages. Algae-based microrobots demonstrated also a greatly enhanced treatment of melanoma lung metastasis through efficient active local delivery of chemotherapeutic drugs into deep lung tissues.[165] In another study, a macrophage-based biohybrid MMs was found to trigger an antitumor immune response through photopyroptosis. This process not only inhibits tumor growth but also prevents lung metastasis.[166] In recent breakthroughs, magnetically controlled NMs have been employed for precise lung injury therapy.[167] These NMs exhibited high biocompatibility and minimal toxicity while inducing an oriented cytokine storm that induces immune cell hyperactivation.

MMs and NMs offer promising possibilities for lung-related treatments, particularly by enhancing the mucus penetration in pulmonary diseases. Nevertheless, the complex architecture of the lung, along with the difficulty of controlling motor movement within the alveoli, presents challenges. While current research on MMs and NMs for lung applications remains limited and requires further investigation into safety and efficacy, these systems hold considerable promise for future advancements in pulmonary therapies.

5.1.4. The Bladder. The bladder presents an optimal site for the administration of NMs.[168] Its simple anatomical structure, where liquid is confined and its direct access via the urinary tract, facilitates precise administration, eliminating the need for invasive or intravenous procedures. This, combined with the absence of high fluid flows or complex matrices, minimizes potential obstacles and interactions that can hinder the motion of the NMs. Recent advancements have introduced different methods for treating bladder diseases. For instance, MMs has been employed for photothermal therapy, to destroy bladder cancer cells using NIR irradiation[169,170]

For instance, chemodynamic therapy (CDT) has introduced a treatment strategy by converting intracellular hydrogen peroxide within tumors into reactive oxygen species (ROS) to kill cancer cells. Leveraging this approach, NIR light-powered NMs have been used in combination with a chemodynamic therapeutic agent, demonstrating significant motion capabilities, enhanced penetration depth in the bladder wall, and effective CDT action.[170] Besides, magnetic control has also been explored for bladder cancer treatment by Cong et al. They developed magnetic-powered Janus cell MMs incorporating oncolytic adenoviruses, which selectively infect and replicate exclusively within cancer cells. This approach

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achieved enhanced tumor suppression *in vivo*, improved tissue penetration, and extended residence time in the bladder compared to passive delivery, which lack directed movement of therapeutic agents.[171] However, most NMs for treating bladder diseases are enzyme-powered, specifically utilizing urease. The efficacy of urease-powered NMs is particularly notable due to their ability to use the environment of the bladder for enhanced therapeutic action. By catalyzing the hydrolysis of urea present in the urine, these NMs can self-propel and improve their distribution within the bladder cavity, thus, enhancing their therapeutic potential. Urease-powered NMs have shown significant penetration in mucosa layer of the bladder wall,[172] in 3D bladder cancer spheroids[15,168] and *in vivo* bladder tissue,[25] demonstrating their effectiveness. Their collective motion was monitored within bladders of living mice using imaging techniques, including positron emission tomography−computed (PET-CT)[25] and photoacoustic imaging.[173,174] Furthermore, they also demonstrated promising results for cancer treatment in preclinical studies, achieving a remarkable 90% tumor reduction in mice bladders with a single administration (Figure 6d).[11] These promising outcomes indicate the potential of NMs as a therapeutic strategy in the treatment of bladder diseases, providing a noninvasive and highly effective alternative to traditional therapies.

The application of MMs and NMs in the bladder shows promising potential for active navigation within this cavity. Although challenges arise due to the dynamic environment, including urine flow and pH variations, studies—particularly in animal models—have demonstrated encouraging results. These findings suggest significant clinical viability, especially for motors propelled by biocatalysts.

5.1.5. The Joint. Joints are among the tissues that can be directly accessed and are often affected by diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA).[175] These conditions can cause severe pain and loss of function, significantly impacting the quality of life. Mesenchymal stem cells (MSCs) have demonstrated promise in treating and repairing joints damaged by OA, due to their regenerative properties.[176] However, the presence of viscous fluids in the joints, such as SF, can reduce the effectiveness of these therapies.[177] The use of magnetically guided NMs combined with MSCs that are loaded onto microscaffolds for noninvasive treatment is one of the explored strategies to solve this issue. These MSCs, when cultured with transforming growth factor-β1, have demonstrated chondrogenic potential, which indicates their ability to repair cartilage in cases of OA, *in vitro*,[178] and human adipose-derived MMs for targeted cell delivery in cartilage regeneration *in vivo* (Figure 6, e).[179] Recent treatments for RA have employed NMs, with some therapies focusing on hydrogen as a key agent for scavenging reactive oxygen species (ROS) and reducing inflammation. In that sense, magnesium-based MMs were used to decrease pro-inflammatory cytokines. The hydrogen generated by these MMs propelled them and helped to mitigate RA progression by neutralizing ROS and reducing inflammation, both *in vitro* and *in vivo*.[180] Other therapies targeted the overproduction of H_2O_2, a ROS that is often elevated during RA. Excess H_2O_2 can exacerbate oxidative stress and inflammation in the affected tissues, contributing to the progression of the disease. These NMs aimed to reduced H_2O_2 levels and generated O_2 *in situ*, functioning as detectors of inflammation, propellants for enhanced diffusion, and mitigators of the hypoxic synovial microenvironment. This approach relieved bone and cartilage degradation in joints *in vivo*.[12]

Overall, the use of MMs and NMs shows significant potential for noninvasive treatment of joint diseases like OA and RA. These therapies have demonstrated effectiveness *in vitro* and *in vivo*, offering new hope for cartilage repair and inflammation reduction.

Although motors must overcome the highly dense SF within the joint, recent strategies to modulate this medium and enhance particle propulsion are promising for future clinical applications, particularly for transporting drugs into cartilage. While further research is needed in this field, exploring various materials for this purpose appears highly encouraging.

5.1.6. The urogenital tract. In recent years, sperm-based MMs or "spermbots" have emerged as a novel strategy to assist sperm cells with motion deficiencies or low sperm count in reaching the oocyte for *in vivo*-assisted fertilization[181] and serving as targeted drug delivery systems for cancer treatment.[182] These carriers have shown promising results in transporting a single sperm cell. For instance, sperm-driven MMs, consisting of a sperm cell attached to a magnetic microtube, can navigate the fluid within the bovine reproductive tract at varying velocities influenced by fluid viscosity.[183] Researchers have also explored optimizing microcapsule with different shapes to enhance the flagellar beat frequency and propulsion of motile spermatozoa and improve their locomotion.[184] Additionally, biohybrid magnetic MMs, known as IRONSperms have been developed by coupling nonmotile sperm cells to magnetic NPs to power and control their motion. This is achieved through electrostatic self-assembly, which uses sperm cells as a biotemplate to create soft and flexible MMs for mimicking their natural motion with speeds up to 6.8 um/s.[185] Recently, a new generation of 4D-printed multifunctional microcarriers has been introduced for assisted reproduction (Figure 6, f).[186] These carriers can transport multiple motile sperm cells and heparin, which enhance sperm motility by inducing physiological changes and increasing metabolism. They exhibit temperature-sensitive behavior that affect sperm hyperactivation. Furthermore, these carriers are loaded with the hyaluronidase, an enzyme that digests the extracellular matrix of the cumulus cells that surround the oocyte, thereby improving target delivery. While these advancements represent a significant progress in assisted fertilization, further enhancements are needed before advancing to *in vivo* trials.

For this particular application, motors reported in the literature have demonstrated effective drug loading alongside sperm cells, which may aid in fertilization. Significant advances, particularly in developing temperature-sensitive motors that enhance sperm hyperactivation, combined with the ability to target them via an external source (e.g., an external magnetic field), propel these innovations toward future clinical trials to address fertility disorders.

5.2. Locations Indirectly Accessible. *5.2.1. The Stomach.* The stomach is a unique organ characterized by a highly acidic pH 1.5−2.5.[187] This property has been utilized for the application of MMs with acid-driven propulsion. These MMs can dissolve in gastric acid, releasing a preloaded cargo. A decade ago, in 2015, the first *in vivo* study on mice demonstrated the potential of zinc-based tubular MMs for targeted stomach delivery.[100] The MMs were administered by using gavage, and subsequent observations revealed successful tissue penetration and retention, attributed to the propulsion

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of the MMs within the stomach. Furthermore, their gradual digestion facilitated a controlled release of cargo over time. A year later, tubular MMs composed of Mg coated with a commercial polymer, Eudragit L100−55, was developed for targeted delivery to the gastrointestinal tract.[188] This polymer protects the MMs from gastric fluid (pH 1−3) and dissolves in intestinal fluid (pH 6−7), ensuring cargo release in this intestine. The dissolution time and consequently the MMs movement duration can be controlled by adjusting the polymer thickness, improving tissue penetration and retention at the desired site. Photoacoustic computed tomography (PACT) has been used to observe and guide Mg-based MMs within the *in vivo* intestine.[189] The motion of these MMs, which covered a distance of 1.2 cm, was monitored over approximately 7 h. These results pave the way for new possibilities of more effective stomach treatments using MMs. Indeed, in efforts to combat gastric bacteria, the authors hypothesized that MMs could play a potential role in eradicating these pathogens. They tested this by loading their Mg-based MMs with a clinically approved antimicrobial drug.[102] Upon successful release of this drug into the stomach of a live mouse model, there was a notable reduction in *H. pylori* infection, with the infection rate being 2.3 times lower than in the control group, that did not receive MMs treatment. This demonstrates the potential of MMs as an effective tool for combating gastric bacterial infections. The reaction of the Mg engine of Janus motors with the gastric fluid has been shown useful for rapid proton depletion toward neutralizing the acidic environment of the stomach, for making these MMs attractive alternative to proton pump inhibitors.[190] Active propulsion and delivery of antigens, based on toxin-functionalized Mg-Janus MM, was shown useful for enhancing immune stimulation against the antigenic payload.[191]

A limitation of current MMs is their brief propulsion lifetime within the gastrointestinal tract. To address this issue, an algae-based capsule motor has been developed by Wang et al.,[192] demonstrating up to 12 h of continuous motion in a simulated intestinal fluid (Figure 6g). This indicates prolonged retention and sustained doxorubicin release within the *in vivo* gastrointestinal tract. Similarly, green algae functionalized with macrophage membrane−coated NPs were recently shown to be extremely useful for "on-the-fly" neutralization of proinflammatory cytokines toward greatly enhanced treatment of inflammatory bowel disease (IBD).[193] Stomach protection strategies using pills are evolving and being applied to various motors, including those that are Zn-based, Mg-based, and algae-based. These strategies employ pH-sensitive polymers, porcine gelatin, and lactose, among others, refining the actual translation for biomedical applications in the stomach.[194]

Alternative MMs for active oral drug delivery were developed using urease to self-propel them, avoiding the nondegradable residue left by metals like Zn and Mg in the gastrointestinal tract.[195] Urease-functionalized polydopamine−silica-based MMs demonstrated effective motion in acidic gastric fluid and mucin gel. Upon oral administration, these materials showed enhanced penetration and prolonged retention for up to a day.

The numerous successful *in vivo* results reported over the past decade make this application one of the most promising for advancing clinical trials. It offers both effective drug loading and controlled release within the stomach along with capabilities for biofilm disruption.

5.2.1.1. Micromotors-Based Oral Pills. While oral administration is the most common and simple approach for drug delivery, it often suffers from low dosing efficiencies and limited bioavailability due to poor drug absorption. Recently, MMs have been embedded within conventional oral pills to achieve controlled transport and release in the stomach. By integrating active transport properties with a common lactose/maltose oral pill matrix, these oral robotic pills improve drug absorption and bioavailability.[194] The inactive lactose/maltose, matrix ensures protection of the drug-carrying MMs.[196] Additionally, Wang et al. introduced microstirring pills by coencapsulating Mg microstirrers as excipients within conventional lactose/maltose formulations, alongside the therapeutic payload. This offers localized fluid dynamics and efficient mixing action toward faster pill dissolution profiles with enhanced dispersion and bioavailability of the therapeutic payload.[197] These capabilities significantly enhanced the bioavailability of aspirin in a large animal (pig) model. The integration of different MMs functions within oral pills holds promise for developing sophisticated multifunctional pills, leading to more effective drug delivery strategies.[194,198]

5.2.2. The Brain. The blood−brain barrier (BBB), a cellular structure, precisely regulates the central nervous system's microenvironment, posing a significant challenge to efficient delivery of therapeutics agents to the brain.[199] Recently, NMs have been employed to overcome this hurdle, leveraging biointerface modulation and self-propulsion capabilities.

Asymmetric polymeric vesicles encapsulating glucose oxidase and catalase enzymes have been used as a strategy for self-propulsion in response to an external glucose gradient, displaying chemotaxis (Figure 6h).[23] Coupled with the low-density lipoprotein receptor-related protein-1, these NMs demonstrated a 4-fold increase in brain penetration efficiency compared to that of passive NPs. An alternative approach employs polymeric NMs, which are a fusion of synthetic polymers and peptides.[200] These motors are loaded with nerve growth factor, serving as a therapeutic agent for spinal cord injuries. The chosen synthetic polymer exhibits zwitterionic behavior, ensuring excellent biocompatibility and facilitating the NMs' traversal through biological barriers. These NMs reduced inflammation and oxidative damage in an *in vivo* rat model, effectively treating lesions caused by spinal cord injuries.

Due to the high complexity of the BBB and the limited number of motors currently able to cross it without causing unintended damage, this application remains distant from a realistic clinical scenario. However, enhanced motility may position these motors as a promising alternative to traditional NPs, which often become trapped in the BBB, thus, limiting the amount of drug that reaches the target site.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

To date, MMs and NMs have reached a significant milestone of 20 years since their first appearance. During this time, they have undergone notable transformations, progressing from their initial development and simple operations in test tubes to achieving autonomous mobility and multifunctional capabilities for performing complex operations in diverse biological systems. These advances led to major breakthroughs in various biomedical applications. Recent research findings, discussed in this review, have illustrated the versatility and potential of modern MMs and NMs in addressing diverse medical targets, including bladder, stomach, lung, joint, and skin applications.

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They have demonstrated remarkable *in vivo* results and the ability to overcome and operate efficiently in complex media. These accomplishments have been made possible by sophisticated fabrication and characterization techniques, which have enabled the creation of advanced MMs and NMs and the exploration of their intricate interactions with biological interfaces. Notably, methods such as rheology, microscopy, and liquid chromatography have played key roles in these advancements.

In function of the propulsion mechanisms, MMs and NMs must overcome different challenges toward their clinical translation. Magnetic, light-driven, and ultrasound-powered motors are extensively used, as discussed in previous sections. However, these propulsion methods rely on external control systems, which can be challenging to generate and sustain within the body. Additionally, issues such as limited penetration depth in biological tissues affect both light- and ultrasound-powered motors, reducing their effectiveness in clinical applications. Chemical and enzyme-powered motors also encounter barriers to clinical translation. Chemical motors, for instance, can autonomously navigate to target sites and penetrate biofilms, but they mainly rely on chemical fuels (e.g., hydrogen peroxide) to operate, which pose toxicity risks and limit their availability *in vivo*. Enzyme-powered MMs and NMs offer a biocompatible alternative as they can disrupt viscous environments and biofilms by degrading extracellular matrices. However, they also face challenges regarding enzyme stability, potential immune responses, and limited fuel availability. Additionally, both chemical and enzymatic propulsion mechanisms struggle to maintain consistent, directional, and controlled motion within the complex environments of the human body.

Looking ahead, we anticipate that NMs will realize their full potential in biomedicine by overcoming the final hurdle that separates them from clinical trials. However, it is crucial to address various challenges and considerations in their development and clinical deployment. First, the scientific community must prioritize the exploration of NMs poised for regulatory approval. For instance, poly(lactic-*co*-glycolic acid) NPs or other materials which have already received FDA approval for specific molecular weights and applications could serve as a structurally integral core for fabricating NMs. Furthermore, efforts must be directed toward ensuring the scalability, biocompatibility, and biodegradability of the NMs. With proper attention to these major issues, we envision micro- and nanoscale motors being adapted as a new line of active drug delivery vehicles for treating various diseases. One straightforward strategy to validate NMs as nanocarriers is to combine them with already accepted active principles and test the improved efficacy. Control experiments with the free active principles or those bound to passive particles are needed for a realistic comparison. The route of administration is something to be carefully considered as motion may only have a key role in short length-scales but not able to compete with bloodstreams, for instance. Discussions with clinicians and an understanding of the medical needs are also crucial for this field of research.

In conclusion, this Review serves as a roadmap for researchers, guiding them through the current landscape, challenges, and prospects of NMs, fostering a deeper understanding of their potential in biomedicine and toward shaping the future of nanotechnology. Entering a new era in the medical sciences, NMs hold tremendous potential to revolutionize drug delivery and therapeutic interventions. Their future integration into clinical practice promises unprecedented precision and efficacy in advanced treatments. The coming decade will be marked by discovery and innovation, with NMs leading the transformation of disease treatments. The future of NMs in nanomedicine is not just promising, it is here, and it is ready to change the biomedical field.

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Notes

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VOCABULARY

Nanomotor: Nanoscale device that converts energy into motion or mechanical work.

Propulsion: The act or process of driving or pushing something forward using force, often generated by engines, motors, or other mechanisms.

Microrobot: Tiny, often autonomous device designed to perform specific tasks or operations at a microscopic scale, typically within confined or delicate environments.

Nanomedicine: Branch of medicine that uses nanotechnology to diagnose, treat, and prevent diseases at the molecular and cellular levels, enabling targeted drug delivery, among others.

Biohybrid: System combining biological elements (e.g., cells) and synthetic components, powered by multiple energy sources.

Biological barrier: Natural structures in living organisms, like skin, blood-brain barrier, or cell membranes, that control substance movement between body compartments.

Viscous media: Substance or environment characterized by high resistance to flow, where internal friction significantly affects the movement of particles, fluids, or objects within it.

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