Engineering Magnetic Micro/Nanorobots for Versatile Biomedical Applications

Longchen Wang, Zheying Meng, Yu Chen,* and Yuanyi Zheng*

With the rapid development of micro/nanomanufacturing technology, a variety of multifunctional micro/nanorobots have emerged. In particular, magnetic actuation-based micro/nanorobots have attracted much interest due to their advantages of untethered contact, remote control, noninvasiveness, and high tissue-penetrating capability. Various magnetic micro/nanorobots have been designed and applied in biomedicine, which indicates the great potential of clinical transformation. This article reviews the new advancements of engineering magnetic micro/nanorobots for versatile biomedical applications, ranging from targeted delivery, minimally invasive surgery, cellular and intracellular measurement, and intelligent sensing to detoxification and antibacterial applications. The controllability, visualization, and biosafety aspects of magnetically manipulated micro/nanorobots are summarized. In particular, the challenges being faced are discussed to outlook future prospective development.

1. Introduction

In the late 1950s, Richard put forward the fantasy of “swallowing a surgeon” and prospected surgical microcooperation inside the human body. With the development of biomaterials, engineering, medicine, and other disciplines, intriguing micro/nanotechnology developments have been achieved, and numerous small-scale robots have been fabricated.[1–7] Considering that physiological conditions are highly complex and that the motion of scaled-down robots in the low Reynolds regime is governed by viscous forces rather than inertia, various propulsion techniques for improving locomotion efficiency have been developed.[8–11] The driving modes can be divided into internal chemical propulsion and external propulsion, including ultrasonic, optical, electric, thermal, and magnetic forces and their combinations.[12–20] Although tremendous advances have been achieved, there still exist many challenges and critical issues, including integration of the sensing and actuation system at the micro/nanoscale level, the lack of effective adaptable locomotion capability and efficient real-time image monitoring means in vivo, and insufficient biocompatibility, which greatly hinder these micro/nanorobots when aiming toward clinical translation for various disease treatments.

Compared with those driven by other actuation methods, magnetic actuation-based micro/nanorobots have attracted a variety of research interests and have been developed rapidly in recent years because of their inherent advantages, including remote control, untethered contact, engine-less and fuel-free navigation, insensitivity to biological substances, and precise positioning capability.[21–26] In addition, the multifunctionality of synthetic materials, various shape designs, and different magnetic control methods endow magnetic micro/nanorobots with versatile application possibilities. From the varied perspectives, currently available magnetic micro/nanorobots can be divided into several distinctive types. Depending on the design theory, these robots can be categorized into natural/biological, artificial, and biohybrid types.[27,28] Based on specific tasks, magnetic robots have been designed with different morphologies, such as wire-shaped, coil-shaped, U-shaped, rod-shaped, 3D sphere-like, helical-shaped, and fish-shaped robots.[12,29–35] Corresponding to the hardness of the texture, there are soft/flexible robots, rigid robots, and rigid bodies with flexible joints/tails.[23,32,36,37] Referring to the motion trajectory inspired by biological movements in nature, magnetic micro/nanorobots have imitated or directly utilized nematodes, spirulina, bacterial flagella, jellyfish, inchworms, or sperm.[23,37,38–41] Nevertheless, the most indispensable and imperative aspect in designing micro/nanorobots is the capability to move or execute specific tasks.

Due to the rapid development of magnetically manipulated micro/nanorobots, there are many new advancements in this field. Previous publications on magnetic micro/nanorobots were limited to certain aspects, such as imaging technology,[42] robots

Dr. L. Wang, Dr. Z. Meng, Prof. Y. Zheng
Department of Ultrasound in Medicine
Shanghai Jiaotong University Affiliated Sixth People’s Hospital
Shanghai 200233, P. R. China
E-mail: zhengyuanyi@sjtu.edu.cn

Dr. L. Wang, Dr. Z. Meng, Prof. Y. Zheng
Shanghai Institute of Ultrasound in Medicine
Shanghai Jiao Tong University Affiliated Sixth People’s Hospital
Shanghai 200233, P. R. China

Prof. Y. Chen
Materidicine Laboratory of Shanghai University
School of Life Sciences
Shanghai University
Shanghai 200444, P. R. China
E-mail: chenyuedu@shu.edu.cn

*The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/aisy.202000267.

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DOI: 10.1002/aisy.202000267
2. Synthesis of Magnetic Micro/Nanorobots

2.1. Magnetization of Micro/Nanorobots

To fabricate magnetic micro/nanorobots, magnetic materials have been studied in depth in biomedical applications because of their inherent properties of being guided by a magnetic field and being visualized by various imaging modes simultaneously. Depending on their magnetic properties, these materials can be divided into diamagnetic, paramagnetic, ferromagnetic, and superparamagnetic materials. Based on the magnetic components, the magnetic materials used include iron oxide nanoparticles (NPs), nickel (Ni), neodymium–iron–boron (NdFeB), platinum (Pt), CoFe2O4. In addition, natural microorganisms in nature such as magnetotactic bacteria are important sources for magnetizing micro/nanorobots.

One general way to fabricate magnetic micro/nanorobots is to use magnetic materials as a surface covering. This type of robot usually has integrated functional blocks. In one study, a 3D burr-like porous spherical structure was designed to improve the cell-carrying and magnetic actuation capability of microrobots, with a Nickel coating for magnetic actuation and a Titanium coating for biocompatibility, to deliver targeted cells in vivo under a gradient magnetic field-driven mechanism (Figure 2A). The delivered cells could pass through microvessels to arrive at the targeted area and be spontaneously released from the microrobots to the desired site in vitro and in vivo, including in zebrafish embryos and nude mice. In addition, spirulina morphological magnetic microrobots were confirmed to be effective in chemophotothermal cancer therapy, which consisted of core–shell-structured Pd@Au NPs and doxorubicin (DOX) and were covered with magnetite (Fe3O4) NPs on the surface. Microalgae-based multifunctional superparamagnetic helical microswimmers were fabricated by dip-coating Fe3O4 suspensions to obtain magnetism (Figure 2B). In addition, it is meaningful to combine the biological inspiration in nature to make up for the shortcomings of existing synthesis methods. Natural microorganisms or swimmers have been identified as ideal templates, which can be directly utilized as propellers or mimicked by the use of flexible tails by artificial materials, especially the helical structure mimicking prokaryotic bacterial flagella and wave-like movements mimicking eukaryotic spermatozoa and cilia. Bacteria have been immensely utilized as actuators or mimicked in the design of biohybrid microswimmers due to their advanced propulsion and controllability, such as Escherichia coli bacteria attached to the surface of magnetic drug-loaded polyelectrolyte multilayer (PEM) microparticles (Figure 2E). The bacterial flagella of Serratia marcescens was utilized as the forward power for magnetic microbeads coated with streptavidin and Helicobacter pylori was mimicked and coated with urease enzymes to penetrate mucus. A morphologically appropriate mesoporous silica microtube loaded with antibiotic drugs could be incorporated into non-pathogenic Magnetospirillum gryphiswaldense (MSR-1) to target an infectious matured E. coli biofilm manipulated by an external magnetic field, demonstrating high potential for antibiofilm applications.

Magnetic particles can also be encapsulated into versatile carriers to fabricate robots with different morphologies and biological characteristics, imparting the robots with a “camouflage appearance” to enable adaptability to the surrounding environment and locomotion in various media. Hard magnetic NdFeB microparticles were embedded into soft-active materials composed of silicone elastomer, which could be actuated to enable desired shapes to walk/crawl/rotate/jump across obstacles and execute “cargo grasp, delivery and release” tasks like large-scale robots. Manipulated by an exogenous magnetic field, the magnetoelastic membrane could rapidly switch...
between a flat and twisted morphology without alteration of its chemical or mechanical environment. A soft robot with NPs embedded in polydimethylsiloxane (PDMS) featured the capability of precise navigation in a complex and restricted environment. In addition, magnetic iron oxide NP chains incorporated into the microgel shell were utilized to deliver drugs in the microvasculature (Figure 2C). Cells within the human body can also act as carriers of magnetic particles because of their biological features, such as the deformability of erythrocytes and the chemotaxis of macrophages in the tumor microenvironment. Liposomes encapsulating magnetic particles and therapeutic anticancer drugs can be internalized by macrophages to form cell-based microrobots, which can be guided to locomote along a predesignated route under a uniform rotating magnetic field. Erythrocytes encapsulating superparamagnetic iron oxide nanoparticles (SPIONs) retained their deformability and attachment stability even after squeezing in microchannels smaller than their sizes. Furthermore, biomimetic magnetic nanocarriers with platelet membranes demonstrated profound adaptability for targeted delivery in blood vessels (Figure 2D).

Moreover, 3D printing technology endows micro/nanorobots with morphological diversity, and the deformation capacity of soft materials under magnetic manipulation provides the possibility for complex locomotion. By using this technology, Kim’s team reported soft materials printed with programmed ferromagnetic domains to realize complex movements and diverse functions via remote magnetic actuation. Several methods such as self-scrolling, direct laser writing (DLW), glancing angle deposition (GLAD), template-assisted electrodeposition (TAE), biotemplating synthesis (BTS), and two-photon polymerization (TPP) have been utilized for the 3D fabrication of artificial structures (Figure 2F).

2.2. Morphology and Texture of Magnetic Micro/Nanorobots

In addition to the improvement of manufacturing process and material performance, the design theory is also important for the synthesis of micro/nanorobots. The morphology and texture are of significance in the magnetic manipulation of micro/nanorobots in fluid environments which is closely related to the propulsion speed or efficiency. Regarding texture, flexible magnetic robots have the advantages of deformability and maneuverability, high mobility, and versatile movement trajectory that can be subtly altered by changing the magnetic field. To fabricate flexible magnetic micro/nanorobots, hinged or multi-linked structures have been evaluated to obtain high propulsion...
efficiency. A polyelectrolyte bilayer hinge between metallic nanorods imparted the nanostructures with flexibility and the additional possibility of magnetically actuated bending of these nickel-incorporated magnetized nanorods.[83]

In regard to magnetically manipulated microrobots, helical structures were once considered the most effective morphology for microswimmers. Artificial bacterial flagella (ABFs) have been intensively researched in biohybrid robots as an effective solution for the propulsion of micro/nanorobots in Newtonian fluids. However, the propulsion efficiency of different morphologies will vary, even among bionic structures. The morphology of soft microrobots composed of thermally responsive hydrogels was reported to change shape as near-infrared (NIR) laser heating was applied; then, a bilayer tubular head and monolayer helical flagellum could change from a long slender form to a stumpy form with a flagellum wrapping the head, with the former exhibiting a higher forward speed.[82] In addition, benefiting from the increased precession angle of the motion based on the coupling between the rigid head and flexible planar tail, the specially designed magnetic swimmer obtained a high propulsion speed superior to that of helical tails. Achiral planar structures[83] and randomly shaped aggregates[84,85] have been demonstrated to successfully and efficiently steer through liquid under the control of a rotating magnetic field. To find the optimal shape of a bioinspired magnetic corkscrew,[86] Mirzae and coworkers introduced the propulsion efficiency $\delta^s$ as a complementary definition, which was more compelling than the previous definition, as it rectified the maximal speed in body lengths per unit time. The authors demonstrated that the morphology of the $\delta^s$-optimal propeller strongly deviates from the bioinspired slim helix and finally results in a surprising chubby skew-symmetric shape.[21]

### 3. Controllability of Magnetic Micro/Nanorobots

#### 3.1. Magnetic Systems for Micro/Nanorobot Regulation

To precisely manipulate micro/nanorobots to perform different tasks, various magnetic systems have been developed to energize the robots by changing the magnetic force or magnetic torque. According to the method of magnetic field generation, magnetic actuation systems can be classified into electromagnetic actuation systems and permanent magnetic systems.[87]

The electromagnetic actuation system mainly utilizes electromagnetic coils to generate a gradient magnetic field or uniform magnetic field (Figure 3A). With the advantage of altering the strength and type of the magnetic field freely by changing the amplitude and direction of the current, electromagnetic coils can realize precise control of micro/nanorobot movement. For example, 3D Helmholtz coils were deployed to generate a rotating magnetic field for propulsion of helical swimmers,[27,88–90] micromotors,[91] and magnetic swarms.[92] The oscillating magnetic field and on-off magnetic field generated by the electromagnetic actuation system could also be utilized to regulate the movement of magnetic swarms or swimmers.[93,94] Other electromagnetic systems including OctoMag,[95] MiniMag,[96] and Maxwell coil systems[97,98] as well as various types of coils[99–101] were developed to generate adaptable magnetic fields to achieve different functions.

Beyond the specially designed electromagnetic coils, clinical magnetic resonance imaging (MRI) systems, which can perform magnetic particle imaging (MPI), have inspired many researchers’ interests in the actuation of micro/nanorobots (Figure 3B). Martel et al. successfully navigated magnetic beads along a pre-determined trajectory by MRI in vivo, confirming the feasibility of MRI-based actuation.[102] The transportation of therapeutic drugs in a hepatic artery model was realized by MRI gradient coils.[103] The motion of a microguidewire with a magnetic tip in the arteries of an animal was realized by using the fringe field of the MRI system.[104] However, there are still many technical difficulties to overcome for simultaneously manipulating micro/nanorobots under the guidance of MRI, such as developing special actuation sequences.[105]

In addition to electromagnetic actuation systems, permanent magnetic systems with the advantage of minimal heat generation and stronger magnetic fields have been developed and widely used in the actuation of micro/nanorobots in in vivo experiments (Figure 3C). A rotating system with eight magnets for generating a controllable gradient magnetic field was designed to actuate a micromagnet in 3D space.[106] Under the regulation of the gradient magnetic field and rotating magnetic field generated by permanent magnetic systems, microswimmers or micromotors could be propelled forward to perform antibacterial therapy,[107] biofilm removal,[108,109] and cargo delivery.[110]

#### 3.2. Versatile Locomotion of Micro/Nanorobots

Under the manipulation of different magnetic fields, micro/nanorobots with various shapes can generate versatile locomotion modes, which represent the basis of functionalizing magnetic micro/nanorobots in the designated environment. According to the propulsion mode, micro/nanorobot locomotion can be divided into gradient magnetic field propulsion, rotating magnetic field propulsion, and oscillating magnetic field propulsion.[111] The motion mode caused by the gradient magnetic field is relatively straightforward.[88] Under the gradient field diving mode, micro/nanorobots are actuated by the magnetic force, which can be an attractive or repulsive force, to the designated position for various tasks.

However, when driven by a rotating magnetic field, micro/nanorobots with various morphologies can exhibit different locomotion modes. The representative locomotion modes generated are shown in Figure 4. Robots with artificial helical structures or bacterial flagella conducted corkscrew propulsion when actuated by a rotating magnetic field in the vertical direction (Figure 4A).[110,88,112] A microswimmer with a soft silver bridge hinged between a gold “head” and nickel “tail” was propelled forward or backward by rotating the nickel tail.[117] A newly designed asymmetric structural spiral micromotor actuated by a rotating magnetic field was reported to perform gliding and stepping motion.[113] In addition, star-shaped microswimmers,[114] wheel-shaped flaky microswimmers (Figure 4B),[115] Janus sphere micromotors,[116] peanut-like swimming microrobots,[117] and microswarms[92] were shown to exhibit rolling or tumbling propulsion along the direction of magnetic field change. These systems were called “surface walkers,” which referred to micro/nanorobots propelled along the proximal surface.
In an oscillating magnetic field, a nanofish robot manufactured by a gold head, a gold caudal fin and two nickel-made segmented bodies linked with flexible silver performed well in wagging propulsion (Figure 4C). The 3-link swimmer was demonstrated to exhibit higher propulsion efficiency than that of 1- and 2-link swimmers under the same planar oscillating magnetic field. A nanorobot with symmetrical multilink arms could perform freestyle swimming through the alternating swing of two arms actuated by a magnetic field. Surface walker propulsion was also performed by a Janus microdimer manipulated by an oscillating magnetic field. Moreover, a flexible soft robot was propelled through a crawling motion to pass through a narrow channel (Figure 4D). Scallop propulsion is another locomotion pattern actuated by an oscillating magnetic field, and a microscallop-shaped microswimmer was proposed to exploit the fluid viscosity difference caused by its asymmetric opening and closing motion (Figure 4E).

4. Versatile Biomedical Applications of Magnetic Micro/Nanorobots

4.1. Targeted Delivery

Targeted delivery is the foremost issue in biomedical applications. However, the existing delivery system of nanomedicine mainly relies on systemic circulation or in situ subcutaneous injection, which is inefficient and lacks penetration. To solve this problem, magnetic manipulation of micro/nanorobots has shown immense potential; therefore, many studies have demonstrated successful small-scale positioning and delivery with direct and indirect methods. Benefiting from the micro/nanoscale volume, the micro/nanocarriers could arrive at some complex and small regions inside the human body.

Magnetic micro/nanorobots can realize cargo transport through chemical bonding and achieve targeted cargo delivery.
under the control of a magnetic field. Utilizing a platelet membrane loaded with magnetic NPs and L-arginine, biomimetic nanocarriers achieved rapid targeting to the thrombus under magnetic guidance. A sperm-like micromotor chemically bonded with heparin was used to perform cargo transport in blood flow. Magnetic Janus microrollers combined with antibodies and drug molecules on the surface were able to target cancer cells in the circulatory system. In addition, physical loading is another way to deliver cargos. Magnetic microswimmers with multicellular Spirulina structures were used to load, transport, and release fluorescein isothiocyanate labeled bovine serum albumin (FITC-BSA) (Figure 5B). A capsule-type microrobot consisting of a magnetic plunger and a cap could execute a “pick-and-drop” motion to transport certain cells or cargos, in which the cap acted as the container and the plunger could be guided to move the cap forward and backward through a counterclockwise and clockwise rotating magnetic field, respectively. Magnetic microrobots containing mesenchymal stem cells successfully targeted damaged cartilage and realized the regeneration of knee cartilage. To increase the capacity, 3D porous microniches were fabricated as a multicell transporter, which was coated with Ni and Ti for magnetic actuation and biocompatibility. A multicompartmental microsphere (MCM), which could rotate under a highly controlled external magnetic field with magnetic NPs in various predetermined compartments, successfully encapsulated different types of cells for coculturing. A 3D porous structured magnetic microrobot was also developed and showed good ability to...
transport target cells in the yolk of zebrafish embryos (Figure 5D). Target delivery assisted by micro/nanorobots includes not only macroscopic therapeutic or diagnostic molecules and drugs but also intercellular and intracellular biochemical signals at the microscale. Recently, cylindrical magnetic microrobots successfully delivered a photocleavable linker with the signaling molecule N-butyryl-homoserine lactone (C4HSL) to bacterial cells, in which a magnetic field guided the robotic carrier to the targeted site and light exposure actuated the release of the signaling molecule. A diamagnetically levitated robotic system manipulated the loading and delivery of nanoliter fluid volumes in micropipettes at micrometer-scale precision, showing prospects for cell injection and cell surgery. This robotic system successfully addressed specific cell groups with spatiotemporally fine precision and delivered different biochemical signaling cues simultaneously or continuously with independently driven robots.

In addition, magnetically actuated morphological change is helpful for targeted transportation. For example, superparamagnetic microparticles tend to show chain-like arrangements in a magnetic field because of dipole–dipole attractions. This special morphological arrangement of microrobots was capable of transporting single cells with a large size or aggregated morphology, such as T27D, while individual spherical magnetic microbeads...
might fail to transport them. A self-propelled microrobot was fabricated with superparamagnetic iron oxide as the interior core and half-covered Pt as the outside catalytic layer. Guided by an external magnetic field, these superparamagnetic microbeads moved toward suspending cells, and the target cells were successfully captured via binding between the NH₂ group inside the cell membrane protein and the tosyl groups on the surface of the microrobots.

In addition, “fictitious cargo containers” can be realized by microrobots, of which dynamic locomotion under magnetic manipulation could also help execute carrying tasks (Figure 5E). A rotating motion could generate a vortex, which enabled microswarms to capture or carry cargos and then proceed with targeted delivery and execute release action at specific operating frequencies. The larger vortex the swarms could produce, the heavier and larger cargos they could manipulate. Importantly, some fragile protein crystals could be intact and transported by such a fluidic vortex. Through generating a dynamic-equilibrium vortex, clustered magnetic NPs could transport cargos to the target, such as the retina. To improve the targeted delivery efficiency, magnetic micro/nanorobots not only acted as directing carriers of the target cargo but also worked well as “indirect promoters.” For example, the rotational motion of magnetic nanomotors could enhance the interaction between tissue plasminogen activator (tPA) and thrombus (Figure 5F). The larger vortex the swarms could produce, the heavier and larger cargos they could manipulate. Importantly, some fragile protein crystals could be intact and transported by such a fluidic vortex. Through generating a dynamic-equilibrium vortex, clustered magnetic NPs could transport cargos to the target, such as the retina.

In addition to mechanical operation, these robots can be used for the treatment of vascular diseases. A ferromagnetic soft robot accurately reached the deep part of the vasculature under the guidance of magnetic field control, showing a potential application in the treatment of hemangioma. In addition, under the guidance of a magnetic resonance boundary field, a guidewire with a magnetic microtip realized precise navigation in living pig artery vessels (Figure 6E). In addition to drug delivery, magnetic soft micro/nanorobots were observed to gather at a clot site to enhance the magnetic hyperthermia therapy effect and realize the rapid removal of thrombus (Figure 6F). All these contributions provide new solutions for minimally invasive surgery in deep tissue.

4.3. Cellular and Intracellular Measurement

Measuring the mechanical properties of cells is helpful to understand the function of cells and the mechanism of the development of related diseases. In cellular and intracellular measurements, a magnetic force or magnetic moment is applied to magnetic micro/nanorobots (magnetic NPs) acting on the cell or organellae. Through observing the deformation of the cell membrane or organelle structure, such as the cytoplasm, nucleus, and cytoskeleton, the elastic, viscosity, and viscoelastic parameters can be quantitatively analyzed.

Magnetic tweezers (MTWs) have been used as a powerful biophysical tool to generate force and torque to measure cellular mechanical characterization and function. Mechanical plasticity of the cytoskeleton was researched by measuring the plastic deformation when magnetic bead applying force on the cell. A single-molecule magnetic tweezer assay was used to generate force by pulling on the magnetic bead, while matrix metalloproteinase-1 (MMP-1) cleaved collagen. By researching the magnetic bead detachment kinetics, a model in which the collagen trimer unwinds prior to proteolysis by MMP-1 was confirmed.

Except for cellular measurement, intracellular measurement to explore the spatial and temporal activity of subcellular and suborganelle structure is of significance. An intelligent submicrometer magnetic robot was successfully designed to realize intracellular micromanipulation and physical measurements at the spatial and temporal levels. Utilizing a 3D multipole magnetic tweezer instrument, the magnetic bead successfully applied a force up to 60 pN, and the measured force deformation spatially and temporally demonstrated the nucleus stiffness polarity. Recently, the force-induced remnant magnetization spectroscopy (FIRMS) technique was used to measure the cell adhesion force according to the interaction strength of magnetic NPs with cells. By detecting the magnitude of the magnetic signal induced by force, the adhesion force of cancer cells could be calculated. In addition, magnetic helical nanomotors, which were proved to be noninvasive to the cell viability, were controllably maneuvered by rotating magnetic field in the living cells and the motion of these nontoxic magnetic nanomotors were observed to be highly sensitive to the local
mechanical properties of the intracellular environment. The same strategy was used to fabricate Fe–Pt nanopropellers, which realized active cell targeting and cell transfection actuated by magnetic field. These properties indicated promising applications of measuring and probing intracellular biophysical environments by analyzing the motion of magnetic nanomotors.
For example, the local viscoelasticity of the cytoplasm inside living cells was measured by magnetic wires and first demonstrated that the interior biofluid to be as viscoelastic liquid but not as an elastic gel.[144] Magnetic helical nanorobots as mechanical probes realized accurate measurement of cytoplasmic viscosity of HeLa cell.[155]

4.4. Intelligent Sensing

Magnetic micro/nanorobots made of multifunctional materials can automatically sense the surrounding environmental factors, such as temperature, pH, and biomolecules, to accomplish tasks preset. Owing to specific physical and programmable properties, hydrogels have been researched intensively in intelligent sensing applications such as controlled-release systems, while the flexibility to fabricate into self-defined morphology is highly favored in 3D printing microrobots.[80] The micro/nanorobot made of thermosensitive hydrogel encapsulated with magnetic NPs could shrink deformation with increasing temperature (Figure 8A).[156] A magnetic soft microgripper grabbed and released cargos in response to environmental temperature changes (Figure 8B).[138] Magnetic micro/nanorobots based on hydrogel 3D printing sensed the pathological concentrations

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Figure 7. Cellular and intracellular manipulation of magnetic small-scale robots. A) Mechanical plasticity measurement of cell. (i) Magnetic bead was attached to a cell and moved toward the needle tip of magnetic tweezer. (ii) Deformation of actin cytoskeleton when magnetic bead applied force. Reproduced with permission.[149] Copyright 2016, Nature Publishing Group. B) The microbead was navigated to the target position, and the trajectory was recorded as red lines for the measurement of nuclear polarity. Reproduced with permission.[151] Copyright 2019, AAAS. C) Schematic illustration of cell measurement through applying mechanical force to magnetic beads and recording force-induced remanence signal decrease by FIRMS. Reproduced with permission.[152] Copyright 2020, The Royal Society of Chemistry.
of matrix metalloproteinase-2 (MMP-2) and reacted by swelling rapidly, triggering the release of the embedded therapeutics (Figure 8C). The microrobots could also biodegrade and further release antibodies targeting cancer cells. A magnetic microdrill capable of sensing pH changes was fabricated by using a spiral brass wood screw as a spiral-type blade for propulsion and a rectangular NdFeB magnet as a magnetized body to deliver a torque, which showed promise for monitoring diseased tissues. A magnetic field was also utilized as a stimulus factor beyond propulsion, such as magnetic microrobots responding to a hyperthermic environment when exposed to an alternating magnetic field, which helped to open the blood–brain barrier (BBB) to deliver therapeutic drugs. A magnetically actuated micro/nanorobot with a pattern recognition function intelligently perceived obstacles and automatically selected the optimal path to avoid bumping into normal red blood cells (RBCs) and target cancer cells (Figure 8D).

Figure 8. Intelligent sensing magnetic micro/nanorobots. A) Microrobots could shrink to a smaller size in response to high temperature. Reproduced with permission. Copyright 2011, Taylor & Francis. B) Schematic illustration of a magnetic soft microgripper realizing self-folding in response to temperature. Reproduced with permission. Copyright 2017, American Chemical Society. C) Schematic illustration of a swelling microswimmer for the release of cargos in response to pathological concentrations of MMP-2. Reproduced with permission. Copyright 2015, American Chemical Society. D) Real-time path planning and trajectory of an intelligent microvehicle in a mixed cell solution. Reproduced with permission. Copyright 2019, American Chemical Society.
4.5. Detoxification and Antibacterial

Magnetic micro/nanorobots have also been used to detoxify and remove harmful substances, as they have good locomotion and targeting ability under the control of a magnetic field. Mostly, the robots were coated with functional NPs on the surface or chemically linked with drugs to realize the detoxification function. A 3D printing fish-shaped microrobot based on hydrogels with polydiacetylene (PDA) nanoparticle coatings on the surface was utilized for toxin neutralization applications (Figure 9A).\textsuperscript{[158]} Two other kinds of NPs, Pt NPs and iron oxide NPs, were also incorporated for chemical propulsion and magnetic guidance, respectively. Moreover, micromotors with an mSiO\textsubscript{2} layer on the outer surface provided an increased capacity for pollutant collection and could perform environmental monitoring and pollutant degradation simultaneously.\textsuperscript{[160]} In addition to surface modification with nanomaterials or chemical drugs, natural biomaterials such as cell membranes have been used to function- alize robot surfaces to make them more adaptable to the physiological environment. For example, biomimetic helical

![Figure 9](https://www.advancedsciencenews.com)

**Figure 9.** Examples of magnetic micro/nanorobots for detoxification and antibacterial application. A) Artificial magnetic microfish for detoxification. (i) Energy-dispersive X-ray spectroscopy images demonstrating the element composition of microfish body. (ii) Fluorescent images of microfish incubated in toxin melittin solution, demonstrating the detoxification capability. Reproduced with permission.\textsuperscript{[158]} Copyright 2015, Wiley. B) Schematic illustration of platelet motors for toxin binding and pathogen binding. Reproduced with permission.\textsuperscript{[161]} Copyright 2018, Wiley. C) Biofilm removal results utilizing liquid metals under the regulation of magnets with different sizes. The inset depicts a confocal image displaying the boundary of the treated area. Reproduced with permission.\textsuperscript{[108]} Copyright 2020, American Chemical Society. D) Schematic illustration of catalytic antimicrobial robots for biofilm removal (i) and applied to treat biofilms of human teeth (ii). Reproduced with permission.\textsuperscript{[164]} Copyright 2019, AAAS.
nanomotors with platelet membrane cloaking exhibited attractive detoxification capabilities through adsorption and isolation of platelet-targeted agents (Figure 9B).[161]

Magnetic micro/nanorobots can also kill bacteria and remove biofilms through physical or chemical interactions. In one study, magnetic micro/nanorods effectively destroyed a biofilm through physical contact friction.[162] The mechanical force generated by the swing motion of a robot under a magnetic field acted on the pathogens, facilitating pathogen death.[163] In addition, liquid metal NPs could develop sharp edges in a rotating magnetic field, which effectively physically ruptured the biofilm matrix and killed the bacterial cell (Figure 9C).[168] Under the control of a magnetic field, a robot with catalytic function not only destroyed the biofilm but also transported the biomass away to avoid regeneration (Figure 9D).[164] The catalytic antibacterial robot utilized magnetic iron oxide NPs with catalytic functions to produce bactericidal free radicals, decomposing the extracellular polysaccharide (EPS) matrix, and finally removed biofilm fragments by a magnetically driven biofilm device. This 3D printed polymeric soft robot has been applied to biofilm eradication on the internal surface of human teeth. Another PDA-coated magnetic helical microrobot combined with the photothermal effect produced by NIR light was used to treat pathogenic bacterial infections.[107]

5. Visualization of Magnetic Micro/Nanorobots

Benefiting from the visualizing feedback, the motion of magnetic robots could be guided and tracked to realize the functions of targeted transportation and precise mechanical manipulation.[165] With the advantages of intuitive imaging and ease of obtaining images, optical microscopic imaging has been widely used to observe and evaluate the locomotion performance of robot in vitro magnetic control experiments (Figure 10A).[23,26,42] In addition to 2D imaging, researchers have realized the 3D positioning of micro/nanorobots using multiple optical microscopes.[166] At present, most of the research is based on open-loop imaging feedback. Through localizing the position and observing locomotion mode according to the image, further operations were conducted to change the direction and position of the robots to accomplish various tasks. Researchers have combined pattern recognition technology with artificial intelligence algorithms to form closed-loop feedback to automatically navigate robot movement, which has been verified in in vitro experiments.[116] Furthermore, with the advantage of high resolution, optical coherence tomography (OCT) has been utilized to provide image feedback for robots in drug-targeted transport in the eyes.[193]

Fluorescence imaging has also been used to visualize the movement of micro/nanorobots. Combined with the characteristics of the synthetic materials composing magnetic micro/nanorobots, researchers have incorporated a variety of fluorescent tracers, such as autofluorescent materials, NIR fluorophores,[199] organic dyes, and quantum dots (QDs),[167] to realize motion monitoring. Fluorescent calcein-labeled liposomes were integrated into ABF microrobots in Mhanna’s study and showed high fluorescent stability during locomotion.[168] To improve the tracking of fluorescent microrobots under dark field, Steager et al.[169] developed a single-step fabrication process for biocompatible magnetic microrobots using a composite photoresist mixed with iron oxide powder on glass slides. The studies also suggested that autofluorescence had potential for real-time tracking of swimming microrobots. By using intrinsically autofluorescent materials such as microalgae, micro/nanorobots could be localized by using the fluorescence signal, while microalgae were also used as swimming templates (Figure 10B).[27] Moreover, magnetic target delivery can be visualized to observe the delivery order and pattern of the fluorescent cargo.[146] Biohybrid algal microswimmers were connected to polyelectrolyte-functionalized magnetic spherical cargos, and the effective delivery of fluorescent isothiocyanate–dextran molecules into mammalian cells and the 3D swimming movement manipulated by the magnetic fields were clearly recorded.[52] Recently, Zhang’s team utilized fluorescence imaging for visual feedback to realize automatic tracking and navigation of micro/nanorobots for targeted delivery of cargos.[170]

With the development of MPI technology, MRI has been regarded as an appropriate imaging method for magnetic micro/nanorobots, and it was hoped that the magnetic field of this modality could be used to actuate and image the robot at the same time. Accordingly, the good monitoring ability of MRI to localize magnetotactic bacteria has been successfully demonstrated.[173] In addition, Yan et al. fabricated multifunctional superparamagnetic helical microswimmers by dip-coating Fe3O4 suspensions onto Spirulina microalgae, which could be remotely monitored by in vivo fluorescence imaging and tracked inside a rodent stomach by MRI (Figure 10C).[27] Although a clinical magnetic resonance device has been utilized to actuate and track ferromagnetic beads of millimeter grade,[102,172] the current magnetic field gradient in the MRI area cannot meet the needs of driving micro/nanorobots.[173] Thus, it is necessary to develop ultrafast imaging sequences to achieve real-time tracking.[103]

Ultrasound (US) imaging is another efficient alternative for medical robotics, with the capability of deep tissue penetration and real-time feedback. Scheggi[174] demonstrated the wireless magnetic motion control and planning of soft untethered grippers using feedback extracted from B-mode US images. Regarding deep tissue, the robots were still visualized by US when rolling in the concealed areas of ex vivo chicken muscle tissue (Figure 10D).[23] Moreover, benefiting from US imaging guidance, a magnetic helical robot could remove blood clots with an optimal rubbing frequency.[175] However, the locomotive accuracy monitored by US images might be compromised; Scheggi et al. utilized US B-model images as feedback to show the motion of the microjets, and the location accuracy was somewhat lower than that of microscopic image feedback.[174] Combining the advantages of the deep penetration of US imaging and high resolution of optical imaging, photoacoustic tomography imaging (PACT) has been used to monitor the locomotion of micro/nanorobots (Figure 10E).[107]

In addition, with the wide application of magnetic micro/nanorobots, more imaging methods are used to monitor their movement. With high imaging speed and strong penetration, X-rays have been used for real-time imaging and tracking of micro/nanorobots in the treatment of vascular
diseases.\textsuperscript{104} Arthroscopic imaging was applied in an experiment with magnetic micro/nanorobots promoting cartilage regeneration (Figure 10F).\textsuperscript{124} However, the highly penetrating, high-resolution, noninvasive, and real-time imaging methods of magnetic micro/nanorobots still need to be studied.

6. Biosafety of Magnetic Microrobots

6.1. Biocompatibility

Biocompatibility is one of the most important requirements in the design of micro/nanorobots for in vivo applications.
A micro/nanorobot system in vivo application will trigger drastic host responses by the immune system, resulting in the malfunction of the robotic device and the life-threatening risk of platelet activation.[5] Although bacteria have been widely used as propellers in biofluidic environments, their characteristics of fast growth and incompatibility with mammalian cells have limited their application to inner-body cavities and solid tumors.[176]

To overcome cytotoxicity or incompatibility, scientists have developed several methods such as using nontoxic microalgae[32] as a substitution or biocompatible material to cover or directly harness certain somatic cells such as macrophages and RBCs (i.e., erythrocytes) as optimal coatings or carriers.[69]

Among biocompatible coatings, organic polymers such as polyethylene glycol (PEG)[177,178] and gelatin[112] have been intensively used as biocompatible covers, into which superparamagnetic NPs can be assembled to form magnetic biodegradable microrobots. In addition, inorganic coverings, such as Ti[125] and Fe,[179] have been researched, but an exposure risk still exists during the fabrication process, and the coating layer cannot fully cover microrobots. A burr-like porous spherical structure was fabricated for carrying and delivering targeted cells in vivo, with a Ti material coating to enable biocompatibility.[32] The zinc ferrite coatings were deployed on the surface of magnetic nanomotors to against agglomeration.[180] Same strategy was utilized to co-deposit Fe and Pt on the nanopropellers to make them nontoxic and biocompatible (Figure 11A).[154] Nelson’s group used the biocompatible photoresist ORMOCOMP to fabricate highly biocompatible helical bodies.[179] Research[51] has also combined natural bacterial swimmers and RBC cargo-containing magnetic materials to produce an efficient and biocompatible targeted delivery system. To improve the biocompatibility of the bacterial microrobot, autologous RBCs were utilized in the fabricated biohybrid swimmer as carriers for active and controlled delivery, which were used to load anticancer DOX drug molecules and SPIONs steered by an external magnetic field and were attached to bioengineered motile bacteria (Figure 11B).

### 6.2. Biodegradability

If biomedical microrobots cannot be retrieved from the body, degradability will be the foremost issue for in vivo clinical applications. The material properties of robots mainly determine their biodegradability. A porous hollow microswimmer with a superparamagnetic Fe₃O₄-based outer shell and a helical-shaped inner cavity was fabricated in a cost-effective manufacturing process using a biotemplate of the cyanobacterium Spirulina, which turned out to be cytocompatible and biodegradable and could be disassembled into small pieces by ultrasonic stimuli[88] (Figure 12A).

Hydrogel-based materials have been intensively researched in degradable magnetic microrobots because of the feasibility of synthetic modification to obtain degradability.[177] In an in vitro test, the polymer network could be fully degraded in aqueous sodium hydroxide to form sodium polyacrylate (NaPA), a process

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**Figure 11.** Representative examples of biocompatible magnetic micro/nanorobots. A) Schematic illustration of fabrication of magnetic nanopropellers with biocompatible FePt and surface functionalization with polyethyleneimine (PEI) and plasmid DNA. Reproduced with permission.[154] Copyright 2020, Wiley. B) Schematic diagram of fabrication process of RBC microswimmers. Reproduced with permission.[51] Copyright 2018, AAAS.
called saponification.\cite{177} In addition, hydrogel gelatin methacryloyl (GelMA) has attracted researchers’ interest because of its enzymatic degradability, enabling it to be digested by enzymes released by cells after providing support when cocultured with cells (Figure 12B)\cite{80} and digested by MMP-1 in an interesting degradation process in which the hydrogel network first became enlarged in a concentration-dependent swelling process and then collapsed (Figure 12C).\cite{112} Moreover, disulfide bonds are easily cleaved by reduction, so another effective method to achieve degradability in magnetic hydrogel microrobots has been the incorporation of disulfide bonds. A degradable, thermomagnetically responsive micror gripper was delicately designed with a bilayer of two hydrogels incorporating disulfide bonds, and the degradation progress was demonstrated by adding a disulfide-reducing agent—glutathione (GSH);\cite{181} the polymer fragments are nontoxic.

7. Conclusions

The past decades have witnessed significant progress in micro/nanotechnology, biomaterials, and robotic science in the biomedical field, which has promoted the emergence of the interdisciplinary field of micro/nanorobots. Versatile magnetic micro/nanorobots with various shapes and structures have been elaborately fabricated by magnetic surface functionalization of micro/nanomaterials, by loading magnetic materials into various micro/nanocontainers or direct 3D printing, and by utilizing
microorganisms or swimmers in nature. Under the manipulation of various magnetic regulation systems, these robots exhibit diverse locomotion modes, thus realizing the functions of targeted transportation, minimally invasive surgery, cell measurement, intelligent sensing, detoxification, and antibacterial activity. A variety of imaging modalities have been used to monitor and track magnetic micro/nanorobots in vitro and in vivo, and their biological safety has also been investigated. All these studies have promoted the clinical application of magnetic micro/nanorobots in the near future. Although many tentative advances in the field of magnetically controlled micro/nanomaterials have been made, there are still many challenges and unresolved issues hindering our goal to manipulate intelligent magnetic micro/nanorobots with multiple functions to accomplish various tasks (Figure 13).

For the fabrication of micro/nanorobots, the desired magnetic micro/nanorobots require certain unique properties, including distinctive controllability of the motion trajectory, efficient propulsion ability, high magnetic responsiveness, delicate task execution capability, good biocompatibility, and degradability. Every specific design or fabrication of micro/nanodevices has a definite goal. To improve the locomotion performance of magnetic micro/nanorobots and enable specific functions to be achieved, the synthetic materials used are key because the physical characteristics, including shape, texture, structure, and ingredients, can closely affect the responsiveness to the magnetic field and surrounding environment, the capability of executing certain tasks, and the locomotion efficiency and trajectory.[2,182] It is worth noting that the motion in biological environments depends a lot on the surrounding medium, especially the fluid, gel, charge, and so on.[183] The surface modification of magnetic micro/nanorobots is crucial to avoid the aggregation[180] and to improve the locomotion capability in vitreous humor,[9] mucin gel[29] and extracellular matrix (ECM).[184] At present, micro/nanorobots still do not have multiple operation functions like macrorobots. Because it is highly difficult to integrate many mechanical functions on such a small machine, it can only be realized by using multifunctional materials or surface functionalization of materials. Moreover, we think that the lack of differentiation of microrobots and nanorobots might be attributable to their small size compared with commonly used robots, and it might also be due to the limitations of the existing material synthesis technology and the requirements of robot function. There are very few real nanoscaled robots available in literature. With the development of 3D printing technology, more functionalized magnetic micro/nanorobots are expected to be synthesized and there will be necessary of differentiation of microrobots and nanorobots.

In addition, the magnetic manipulation system needs to be further developed to realize better control of the robots. The magnetic field generated by the electromagnetic actuation system is still weak, and the coils will become hot in long-term operation. For permanent magnetic systems, it is difficult to precisely control the change in the magnetic field and the magnetic gradient pulling does not exceed a certain scale.[185] The operation space of both kinds of magnetic actuation systems are constrained, and only in vitro experiments or small animal experiments can be conducted within them. In addition, for multimodality monitoring of magnetic manipulation, high-resolution real-time imaging technology and artificial intelligence technology are expected to be integrated to realize automatic tracking manipulation of micro/nanorobots. With high magnetic field strength and high imaging resolution, the MRI system was once considered an appropriate magnetic regulation system for simultaneous actuation and monitoring. However, clinical MRI systems can only be used to actuate millimeter-scale magnetic robots. Ultrafast imaging sequences need to be further developed to realize real-time tracking.

Figure 13. The summative scheme of the current advances, challenges, and future developments of magnetic micro/nanorobots for clinical translation.
Versatile micro/nanorobots can perform various locomotion modes under the control of a magnetic field. However, the absolute locomotion speed and accuracy of the robot still need to be further improved. The complexity of the physiological environment requires it to have a stronger propulsion ability, and more in vivo tests upon biomedical preclinical applications are urgently needed. Compared with rigid structure robots, 3D printed soft robots can perform diversified motion under the control of different magnetic fields and show improved movement performance. In addition, for more efficient propulsion, the nonspherical magnetic micro/nanorobots possess the capability of multidimensional movement with advantages of measuring and probing biophysical environments at multiple directions and scales. Although individual micro/nanoswimmers can exhibit accurate locomotion performance, tasks often require multiple robots to operate at the same time. Due to the interaction between magnetic robots, the control of collective micro/nanorobots to perform one task independently is still a major challenge. Recently, plasmonic (optical) properties were integrated with magnetic nanomotors for efficient cargo manipulation, providing a new solution for the independent manipulation of multiple nanorobots.

In addition, the biosafety of magnetic micro/nanorobots is an important factor for long-term consideration. When a robot is deployed inside the body, it is considered an intruder. The molecular mechanical effects between micro/nanomagnetic robots and the affected cells, as well as the localization and function of the subcellular structures, have not been effectively studied. Due to their desirable plasticity and biodegradability, hydrogels have recently been extensively used in the fabrication of soft micro/nanorobots. Although existing studies have shown that the synthesized micro/nanorobots have low toxicity and can be degraded, more in vivo experiments are required for verification.

Although there still exist many challenges to overcome, with the development of multidisciplinary technology and mutual cooperation in different fields, the synthesis of magnetic micro/nanorobots will advance toward simplicity and low cost. Combined with the specific application requirements, new magnetically manipulated devices will also be developed and continuously optimized to achieve improved control of micro/nanorobots. Under multimode image monitoring, magnetic micro/nanorobots will be capable of accomplishing various tasks, which will make them more widely used in biomeicine. We foresee that these micro/nanorobots will eventually be applied in the diagnosis and treatment of clinical diseases in the human body in the near future.

Acknowledgements

L.W. and Z.M. contributed equally to this work. This work was financially supported from the National Key R&D Program of China (grant no. 2018YFC0115200), NSFC Key Projects of International Cooperation and Exchanges (grant no. 81720108023), Key Project of the National Natural Science Foundation of China (grant no. 82030050), and Major Projects of Shanghai Municipal Science and Technology (grant no. 2018SHZDZX05).

Conflict of Interest

The authors declare no conflict of interest.

Keywords

magnetic manipulation, micro/nanorobots, micromotors, microswimmers

Received: December 2, 2020
Revised: February 8, 2021
Published online:

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Longchen Wang received his B.S. degree in Biomedical Engineering from Hebei University of Technology in 2009 and M.S. degree in Biomedical Engineering from Shanghai Jiaotong University in 2012. Then he joined Shanghai Jiaotong University Affiliated Sixth People's Hospital as a clinical engineer till 2019. Currently, he is a Ph.D. candidate in Shanghai Jiaotong University. His research includes the development of magnetic actuation platforms for micro/nanorobots, and the design and synthesis of functional nanoplastforms for versus biomecical applications.

Yu Chen received his Ph.D. degree from Shanghai Institute of Ceramics, Chinese Academy of Sciences (SICCAS). He was the full professor in SICCAS. He is now the full professor in Shanghai University. His research focuses on materiacl engineering, nanomedicine, and nanobiotechnology, which involve the design, fabrication, and biomedical applications of 0D mesoporous nanoparticles, 2D nanosheets, and 3D-printing scaffolds. The focused biomedical applications include drug/gene delivery, molecular imaging, chemoreactive nanomedicine, energetic nanomedicine, theragenerative biomaterials, and in situ localized disease therapy.
Yuanyi Zheng completed his Ph.D. study in University of California, San Diego and received his Ph.D. degree from Chongqing Medical University. He is now a full professor in Shanghai Jiaotong University Affiliated Sixth People's Hospital. His research includes the development of magnetic micro/nanorobots for drug delivery and therapy with ultrasound guidance; the design, synthesis, and biomedical applications of polymer, albumin, lipid, and organic–inorganic hybrid ultrasound contrast agents for multimodality imaging, ultrasound molecular imaging, drug delivery, and ultrasound microbubbles-mediated therapy.