Development of micro- and nanorobotics: A review

YANG Jia[1,2], ZHANG Chuang[1,2], WANG XiaoDong[1,2], WANG WenXue[1*],
XI Ning[3] & LIU LianQing[1*]

[1] *State Key Laboratory of Robotics, Shenyang Institute of Automation, Chinese Academy of Sciences, Shenyang 110016, China;*
[2] *University of Chinese Academy of Sciences, Beijing 100049, China;*
[3] *Emerging Technologies Institute, Department of Industrial & Manufacturing Systems Engineering, University of Hong Kong, Pokfulam, Hong Kong*

Micro- and nanorobotic is an emerging field of research arising from the cross-fusion of micro/nano technology and robotics and has become an important part of robotics. Micro- and nanorobots have the advantages of small size, low weight, large thrust-to-weight ratio, high flexibility, and high sensitivity. Due to the characteristics distinguishing from macroscopic robots, micro- and nanorobots have stimulated the research interest of the scientific community and opened up numerous application fields such as drug delivery and disease diagnosis. In the past 30 years, research on micro- and nanorobots has made considerable progress. This article provides a comprehensive overview of the development of these robots. First, the application of the robots is reviewed. Then, the key components of the robots are discussed separately, covering their actuation, design, fabrication and control. In addition, from the perspectives of intelligence and sensing, clinical applications, materials and performance, the challenges that may be encountered in the development of such robots in the future are discussed. Finally, the entire article is summarized, and concepts for future micro- and nanorobots are described.

micro- and nanorobots, magnetic actuation, manipulation, biohybrid robot

1 Introduction

With the rapid development of robot science and technology, applications of robots in the manufacturing and daily life of modern society have become more extensive. The emergence of robots is of great significance to social development and progress. Robots can be divided into a large number of different types, and their overall size ranges from the microscopic to macroscopic scales. In addition, robots of different scales have been developed according to their specific application scenarios. For instance, macroscale robots include industrial robots that can grab and transport cargo [1,2] and that can be applied to welding, assembling, fitting and other

such manufacturing applications [3]; in the service industry, macroscale robots appear on farms [4], hospitals [5], entertainment venues [6] and can be used for cleaning [7]; furthermore, macroscale robots can also be used in military, such as the BigDog, which is designed by Boston Dynamics (Waltham, Massachusetts, USA) specifically for the U.S. military [8]. However, under certain special circumstances, such as in vivo interventional diagnosis and treatment, macroscale robots are not useful due to their large size, which cannot meet the requirements for the manipulation of very tiny objects. Since these robots cannot directly enter into an extremely small space, micro- and nanorobots, which exist and operate on scales as small as micrometers or nanometers, have become increasingly important. These robots can perform tasks on a tiny scale and have great flexibility,

*Corresponding authors (email: wangwenxue@sia.cn; lqliu@sia.cn)

adaptability, robustness and accuracy. They can also work in clusters [9] and display co-operative behavior to accomplish a particular task.

In the past few decades, the development and application of micro- and nanorobots has advanced substantially, giving rise to a new research field. Micro- and nanorobots are commonly used for biomedical applications. For example, micro- and nanorobots with controlled navigation capabilities can deliver drugs that effectively treat diseases by targeting certain locations; such robots even can penetrate tissues [10]. As novel drug delivery platforms, these micro- and nanorobots are usually propelled and/or guided by endogenous or exogenous stimuli toward the area of interest [11]. Chen et al. [12] designed and fabricated wire-shaped magnetoelectric nanorobots that could be precisely steered toward a targeted location by means of wireless magnetic fields and could perform on-demand magnetoelectrically assisted drug release to cells. Garcia-Gradilla et al. [13] developed ultrasound (US)-powered nanowire motors based on a nanoporous gold segment and showed that the nanoporous gold structure can facilitate the near-infrared (NIR)-light-controlled drug release through photothermal effects. Douglas et al. [14] described an autonomous DNA nanorobot capable of delivering molecular payloads to cells and controlled by an aptamer-encoded logic gate, enabling the robot to respond to a wide array of signals such as cell surface markers. Furthermore, Fan et al. [15] showed that gold nanowires conjugated with a cytokine such as tumor necrosis factor-alpha can be transported along any prescribed trajectory or orientation using electrophoretic and dielectrophoretic forces to a specific location with subcellular resolution, promoting the development of controlling signaling events on the single-cell level. In addition, micro- and nanorobots have great prospects for minimally invasive surgery that is highly accurate and reduces the complexity of the surgery. Ullrich et al. [16] carried out experiments in living rabbit eyes and examined the mobility and controllability of a microrobot in different media, showing that microrobots can be a helpful tool for minimally invasive intraocular surgery. Solovev et al. [17] described nanoscale tools in the form of autonomous and remotely guided catalytically self-propelled InGaAs/GaAs/(Cr)Pt tubes. These tubes, with diameters in the range of 280-600 nm, can move in hydrogen peroxide solutions with speeds as high as 180 μm/s. The tubes can transfer chemical energy to translational motion and move in a corkscrew-like trajectory, allowing the tubes to embed themselves into biomaterials such as fixed HeLa cells and enabling their use as minimally invasive surgical tools. Furthermore, micro- and nanorobots have shown considerable promise for precise diagnosis of diseases due to their straightforward surface functionalization and flexible mobile performance. Fischer et al. [18] reported a hybrid microdevice that is powered by ATP and relies on antibody-functionalized microtubules and kinesin motors to transport the target analyte into a detection region with simplified steps and shorter detection time for remote sensing and the diagnosis of diseases. Additionally, miRNAs have been regarded as biomarker candidates in disease diagnosis, leading to the proposal of a nanomotor-based strategy for rapid single-step intracellular biosensing of a target miRNA expressed in intact cancer cells at the single-cell level [19] to allow precise and real-time monitoring of intracellular miRNA expression through the measurement of a fluorescence signal in the cells. In addition, treatment of various diseases is one of the most important goals of biomedicine. For instance, cancer can be successfully treated with the help of micro- and nanorobots. Due to properties such as more targeted localization in tumors and active cellular uptake, nanoparticle therapeutics have gradually evolved into a new type of cancer therapy, offering enhanced efficacy and fewer side effects [20]. Dentistry applications of nanorobots are also notable. Complete dentition replacement therapy, tooth durability and appearance, orthodontic treatment and oral prophylaxis are various potential uses of nanorobots in dentistry [21]. Medical micro- and nanorobots are also used for diabetes control. In these applications, nanobiosensors are embedded in the bloodstream to detect glucose levels and collect information that is transferred to a cell phone as a practical way to interface and communicate with the nanorobots [22]. Nanorobots can also be used for the treatment of genetic diseases by comparing the molecular structures of both DNA and proteins found in the cell to known or desired reference structures, correcting any irregularities and implementing the editing of desired modifications [23]. In the context of practical use of chemical and thermal gradients for biomedical problems, Cavalcanti et al. [24] described the applications of nanorobots in the control of activation for stenosed coronary occlusion. As stated above, micro- and nanorobots have extremely wide applications in the biomedical field, and their use is expected to promote the development of biomedical technology and human healthcare. Among the fields outside medical applications, the application of micro- and nanorobots in the military cannot be underestimated [25]. They can be applied for search, rescue, data acquisition and homeland security. For example, a micrometer-scale helicopter robot equipped with a camera can fly into dangerous areas or areas suffering from disasters to collect information in an environment that would be hazardous to humans; such devices can also potentially be used for spy missions [26]. Moreover, micro- and nanorobots have mechanical applications [27,28] such as nanogears [29], nanojoints [30] and other nanostructures made of carbon nanotubes to assist in the fabrication of complex mechanisms. Micro- and nanorobots can also be used in nano-fabrication, high-end manufacturing and quality monitoring in high-end manufacturing. In the work of Sun et al., they

controlled the number and diameter of nanowires precisely through the operation of nanorobots to ensure that all sensors had the same sensitivity [31]. Besides, micro- and nanorobots play a significant role in environmental engineering and energy security. Kovac et al. [32] designed a bio-inspired aquatic micro air vehicle which can be used for environmental monitoring. To date, the field of micro- and nanorobots has made tremendous progress, affecting a large number of disciplines, and micro- and nanorobots have been applied to many social fields, including surgery, diagnostics [33], personalized medicine, defense and aerospace, automation control and micro/nano electromechanical systems. Therefore, research relevant to the field of micro- and nanorobots has broad prospects for further development and applications.

Micrometer- and nanometer-scale dimensions provide unrivalled advantages to micro- and nanorobots. However, many new challenges have inevitably emerged due to these robots' dimensional characteristics, much more so than in the case of macroscale robots. For example, scaling effects are of concern for micro- and nanorobots, and many studies have been performed in this context [34–37]. When the dimensions of the robots are reduced from macroscopic to microscopic, such as the micro/nano scale, the nature of certain physical laws can be altered due to changes in the surface area-to-volume ratio, and surface area and perimeter-related forces tend to predominate. For example, the water strider insect can float freely on the surface of water without immersion by relying on the surface tension of the liquid rather than the organism's buoyancy [38]. Furthermore, three main contact mechanics models, namely the Johnson–Kendall–Roberts (JKR), Derjaguin–Muller–Toporov (DMT), and Dugdale (D) models, have been proposed [39–41]. With regard to interaction forces between microscale and nanoscale objects, certain adhesive forces such as van der Waals forces [42], capillary forces [43] and electrostatic forces [44] must be taken into account. For instance, Gady et al. [45] analyzed the interaction force gradient between a micrometer-scale polystyrene sphere and an atomically flat highly oriented pyrolytic graphite substrate as a function of surface-to-surface separation distance using an oscillating cantilever technique and found that for distances greater than 30 nm, the electrostatic force due to the charges trapped on the polystyrene sphere dominates, whereas for distances less than 30 nm, the van der Waals interaction is observed. Furthermore, the behavior of micro- and nanorobots is relatively susceptible to temperature, humidity, and fluids. Zhou et al. [46] analyzed two important ambient environment parameters, namely, temperature and humidity, in both theoretical analysis and experimental studies in a typical micro/nano handling environment and provided brief guidelines for microhandling with temperature and humidity consideration. Tambe et al. [47] also studied the effect of relative humidity and temperature on the scale dependence of the adhesive force. The scale characteristics of micro- and nanorobots, that are the physical laws and mechanical properties followed by the robot at the microscopic and nanoscopic scales, are the most basic content in the related research of such robots. Thorough research on basic theory is the basis and prerequisite for the study of other aspects of micro- and nanorobot. Micro- and nanorobots often attract the attention of researchers due to their potential for exploration at the microscale and nanoscale and many applications. At present, The research on micro- and nanorobots has made considerable progress.

In this paper, we review the existing studies relevant to micro- and nanorobots. First, the application of micro- and nanorobots is summarized. Second, the main components of micro- and nanorobots are discussed separately, including a discussion of actuation methods, design strategies, fabrication techniques, and motion control. Multiple types of actuation methods are used for micro- and nanorobots, and for clarity, we have divided the various driving methods into four categories of physical, chemical, biological and hybrid methods. Third, challenges that may be encountered in the future development of micro- and nanorobots are suggested. Finally, the paper is summarized, and the characteristics and required performance aspects of future micro- and nanorobots are conceived.

2   Key components of micro- and nanorobots

The development of micro- and nanorobots is advancing daily. The final formation of a micro- and nanorobot that can be used for practical purposes often requires consideration of several different components, such as actuation methods, design strategies, fabrication techniques, motion control and so on. The study of each component is focused on the common purpose of making the micro- and nanorobot's performance match its application environment. In addition, the renewal of each component of the micro- and nanorobot is expected to significantly enhance the further development of micro- and nanorobots. Hence, some major topics in micro- and nanorobotics are also worthy of attention.

2.1   Actuation of micro- and nanorobots

Over the past few decades, many researchers have made tremendous contributions to the development of micro- and nanorobots, with research in the field advancing daily. In the following, we review micro- and nanorobots based on the variety of actuation methods used for power. Actuation methods of micro- and nanorobots are categorized into physical methods, chemical methods, biological methods and hybrid actuation methods.

2.1.1   Physical actuation

In general, physical motion actuation is realized by magnetism, electricity, light, thermotics, acoustics, and piezoelectricity, among other mechanisms.

Magnetic actuation is widely used for micro- and nanorobots power due to the advantages of strong penetration and remote drive, and magnetic actuation can be used to power the motion of living biological materials in a non-toxic manner [48–51]. For example, the group of Professor Nelson at the Institute of Robotics and Intelligent Systems, ETH Zurich has researched magnetic helical micromachines [52–54]. The helical microrobots are powered and steered in a wireless manner using low-strength rotating magnetic fields, and the shape of the microrobots allows propulsion through various types of materials and fluids, from tissue to different types of bodily fluids. Especially for pipe flow conditions or for 3D swimming in open fluidic environments, helical propulsion is preferred. In addition, different shapes of robots can be chosen depending on the type of motion needed for the application. That group also reported previously unattained in vivo navigation of a swarm of microscale, magnetically actuated swimmers [55] and magnetic nanorobots, a hybrid nanowire, for cancer treatment [56]. The development of magnetic micro- and nanorobots driven by artificial helical or flexible flagella has been inspired by the unique swimming strategies of natural microbes. In addition, micro/nanoswimmers with unique geometries are being developed. For example, Li et al. [57] reported a symmetric multilinked two-arm nanoswimmer that can achieve efficient "freestyle" swimming at low Reynolds numbers. These two-arm nanorobots are capable of an powerful propulsion reaching the speed of up to 12 body lengths per second along with on-demand speed regulation and remote navigation. Moreover, Diller et al. [58] introduced a flexible patterned magnetic material that allows internal actuation, resulting in a mobile micro-gripper actuated by magnetic fields, and demonstrated a gripping motion that can be combined with locomotion by remotely controlling the magnetization direction of each micro-gripper arm; this device is used for 3D microassembly. In addition, magnetic fields can drive organisms. Felfoul et al. [59] have showed that the magneto-aerotactic migration behavior of magnetotactic bacteria, Magnetococcus marinus strain MC-1, can be used to transport drug-loaded nanoliposomes into hypoxic regions of a tumor; and harnessing swarms of microorganisms exhibiting magneto-aerotactic behavior can significantly improve the therapeutic index of various nanocarriers in tumor hypoxic regions. Biohybrid micro-bio-robots have also been developed by capturing bovine sperm cells inside magnetic microtubes that use the motile cells as the driving force and also can be remotely driven by an external magnetic field [60]. However, because magnetron micro- and nanorobots are oriented toward human medical applications, the safety of high-intensity magnetic fields should be considered.

Electric field is typically the preferred mechanism after the magnetic field for the propulsion principle of micro- and nanorobots. Fan et al. [15] have showed that gold nanowires with a length of 6 μm and diameter of 300 nm conjugated with cytokine such as tumor necrosis factor-alpha (TNFα) can be transported along any prescribed trajectory or orientation using electrophoretic and dielectrophoretic forces to a specific location with subcellular resolution. Additionally, the integration of DEP and microfluidic systems offers numerous applications for the separation, trapping, assembling, transportation, and characterization of micro/nano particles [61]. Nanowires with a large aspect ratio that are particularly suitable for use in electric tweezers have also been developed for patterning, assembling, and manipulation with the aid of DC and AC electric fields [62]. At the micrometer scale, Donald et al. [63] presented the use of MEMS actuators for fully 2-D locomotive platforms through capacitively coupled power. Subsequently, a more optimized, untethered, electrostatic, MEMS microrobot was designed with a cantilevered steering arm [64]. The untethered scratch drive is used for propulsion, while the steering arm can be raised or lowered to turn. Furthermore, in micro- and nanorobots research, electric fields can be used not only for propulsion and navigation but also for many bio-syncretic robots, for which there are many other applications. For instance, in the study of the construction of a freely swimming jellyfish from chemically dissociated rat tissue and silicone polymer, the mechanism of symmetric, complete bell contraction can be approximated by electrical field stimulation of electromechanically coupled, anisotropic cardiac muscle (medusoid, bottom) [65]. In addition, living biological cells used to generate driving force in the research of bio-syncretic robots, such as cardiomyocytes, are often used to accelerate the production of functionalities by means of electrical stimulation [66–68]. Moreover, Hwang et al. [69] demonstrated that helical nanobelts can swim in liquid when actuated by an electric field generated by the electro-osmotic force; these devices achieved speeds equal to or slightly greater than those demonstrated by natural bacteria. Additionally, many studies of micro- and nanorobots have been based on electrowetting [70,71]. However, a significant drawback of electric actuation is the presence of electrodes in the work area, which may limit bio-oriented applications.

Light-driven micro- and nanorobots have attracted increasing attention [72–76]. Many light-driven micro/nanotools operate in a similar manner as the corresponding macro tools. For example, Villangca et al. [77] developed a new type of light robot that is capable of loading and unloading cargo such as silica and polystyrene beads using photothermally induced convection currents within the body of the tool. The light-driven nanocar is a synthesized molecule containing a unidirectional molecular motor with the size of

1.7 nm×1.38 nm actuated by a certain wavelength of light [78]. Ibele et al. [79] proposed an autonomous micromotor that moves in deionized water under UV illumination. Huang et al. [80] developed a two-finger microgripper that uses the deformation of a smart material driven and controlled by remote light to actuate one of the two fingers. Beyond that, Ikuta et al. [81] developed optically trapped nanorobots with multiple degrees of freedom and realized remote manipulation of a single cell in liquid with simultaneous reaction force sensing. Ikeuchi et al. [82] also addressed this task at the micrometer scale by developing three key technologies to realize 3D manipulation, imaging and sensing of a single living cell. Glückstad et al. [83] studied light-driven microrobotics, including new and disruptive 3D-printed microtools (termed wave-guided optical waveguides) with six degrees of freedom that can be real-time optically trapped and "remote-controlled" within a volume. In addition to this configuration, light-driven soft microrobots have attracted the attention of researchers. Huang et al. [84] designed and fabricated a soft swimming robot at the micrometer scale with powering and controlling functions provided by a remote periodically flashing UV light and white light. Palagi et al. [85] showed that soft microrobots consisting of photoactive liquid-crystal elastomers can be driven by structured monochromatic light to perform sophisticated biomimetic motions. Even under the driving light, the propeller-type unit can realize monodirectional rotation [86], and plasma nanoparticle transport can also be achieved by an optical manipulation tool [87,88]. An optically controlled bubble microrobot [89] has also been developed. Furthermore, optical driving can be directly used to guide photogenic objects [90,91]. However, some organisms do not possess the property of photo-taxis, and optogenetics can provide light-sensitive properties for these organisms [92,93]. For instance, multiple research groups have developed bio-actuators through light stimulation of optogenetically engineered cells such as skeletal muscle [94–96]. Optical actuation has the advantages of remote control, low noise, and spatio-temporally selective capabilities, for example. This mechanism can also realize local driving and avoid full-field driving. Optogenetic stimuli have especially high spatial-temporal resolution. However, the heat generated by light can damage living biological materials, and penetration of light through tissues should be considered.

Thermal actuation is another common actuation method. By heating the liquid environment where the micro- and nanorobot is located, the micro- and nanorobot can be driven. For example, Magdanz et al. [97] presented flexible thermo-responsive polymer microjets that can reversibly fold and unfold in an accurate manner by applying temperature changes to the solution where they are immersed. Micro-scale objects placed at the air/liquid interface can be actuated by heating the surface of the liquid, as the heat generates a surface tension gradient at the interface, inducing thermo-capillary convective flows that are used to move the micro-scale objects [98]. Moreover, the changing temperature can make the molecule-derived nanocars begin to move in two dimensions through a combination of both translation and pivoting [99]. Rotary nanomotors for which the rotational frequency can be adjusted by varying the temperature have also been developed [100]. Additionally, some microrobots are actuated by the thermal expansion of polyimide [101]. Another type of polymer microrobot, in the shape of a gripper, can also be thermally driven to manipulate biological cells [102]. Gultepe et al. [103] designed so-called μ-grippers as star-shaped microtools that can excise tissue samples from real organs and hard-to-reach locations within a live animal. As mentioned above, micro- and nanorobots are increasingly used in minimally invasive medicine. Note, however, that thermal actuation can cause undesired negative effects, for example, such actuation may cause fatal harm to living organisms or irreversible damage to the materials, making them challenging to recover.

Acoustic actuation is found in a non-negligible share of the studies of the actuation methods of micro- and nanorobots and plays an important role in promoting the development of micro- and nanorobots [104]. Such actuation also provides a large driving force and can achieve more efficient manipulation of micro- and nanorobots. For example, artificial nanoswimmers have been proposed that show high propulsive forces [105]. During acoustic excitation of the nanoswimmer, the tail structure oscillates, leading to a large amplitude of propulsion in traveling waves. Additionally, US propulsion provides a large propulsion force that can overcome the low Reynolds number regime dominated by viscosity, while US imposes little harm on biological samples at MHz frequencies [106]. In other words, acoustic actuation shows favorable biocompatibility and can be widely used in the biomedical field. Because of this compatibility, the use of acoustic methods for manipulation of micro- and nanorobots such as micro/nanoparticles, microspheres, and cells has been extensively studied [107,108]. Additionally, even living biological micro- and nanorobots such as entire organisms (i.e., Caenorhabditis elegans) can be manipulated by acoustic tweezers due to their biological compatibility [108]. Furthermore, micro- and nanorobots driven by US have a variety of styles depending on the purpose. For example, metallic microrods can align and self-assemble into long spinning chains, which in the case of bimetallic rods have a head-to-tail alternating structure and form ring or streak patterns in the levitation plane with US standing waves in the MHz frequency range; the diameter or distance between the streaks is roughly half of the wavelength of the US excitation [109]. Nanowires are another frequently studied structure. To increase the drug loading capacity, Garcia-Gradilla et al. [110] designed US-powered nanowire motors with a tunable

pore size and high surface area; relative to typical nanowires, the incorporation of the nanoporous gold segment was found to increase the active surface area by nearly 20 times. Additionally, it was shown that US-propelled dye-labeled single-stranded DNA (ssDNA)/graphene-oxide (GO) coated gold nanowires (AuNWs) can screen cancer cells based on the endogenous content of the target miRNA [19]. Another kind of US-propelled magnetically guided template-prepared three-segment Au-Ni-Au nanowire motors functionalized with lectin and anti-protein A antibody bioreceptors can capture and transport E. coli and S. aureus bacteria, respectively [111]. In addition to nanowires, nanocups propelled by US have been investigated for drug delivery [112]. Moreover, acoustic microcannons can use nanobullets to drive the drugs directly deep into diseased tissues; such devices can deliver genetic material into cell nuclei for gene therapy [113]. The new US-triggered microbullets that can be loaded with drugs also have the ability to penetrate through dense materials such as kidney tissue for potential targeted delivery applications [114]. The propulsion and manipulation of micro- and nanorobots in cells has attracted increasing research attention and represents the mainstream and urgent need for biomedical advancement. For instance, rod-shaped nanomotors with an approximate diameter and length of 300 nm and 3 μm, respectively, can be activated by resonant US operating at 4 MHz inside living HeLa cells for probing the response of living cells [115]. In addition, the US-propelled nanomotors carrying DNA structures are an efficient tool that addresses the challenges associated with RNA transport and intracellular delivery, increasing the application value of nanobots in gene therapy [116]. The acoustic propulsion of micro- and nanorobots is a fuel-free approach that is expected to greatly aid future medical care. However, US-driven micro- and nanorobots have just begun to emerge, and their development is not mature enough relative to other driving methods. One major challenge when using US is that it does not work well in the presence of bone or gas [117].

Piezoelectrics provide an alternative and attractive method of propulsion generation [118]. Jain et al. [119] developed a microgripper using piezoelectric actuator for handling the miniature parts and carried out the design and analysis of a piezoelectric actuator created by using a combination of two piezo ceramic layers and one resistive layer between them where the voltage (±60 V) is supplied and controlled through a proportional-integral-derivative (PID) controller. Zubir et al. [120] also designed a new piezoelectric-driven microgripper capable of delivering high-precision and high-fidelity manipulation of microscale objects. The use of piezoelectric actuation generally allows fine positioning [121,122], which is a prominent advantage. However, piezoelectric actuation is typically used for slightly larger robots (such as microrobots) and is rarely used for nanorobots.

While the above sections summarize the relevant research

of micro- and nanorobots from the perspective of the physical actuation method, physical actuation methods are not limited to these methods. For example, microgrippers [123–125] actuated by shape memory alloys have been developed. Additionally, some non-gripper-shaped microrobots can be actuated by shape memory alloys [126,127].

2.1.2 Chemical actuation

Micro- and nanorobots also use chemical methods for propulsion, which is one of the typical actuation methods [128–131]. Powered micro- and nanorobots can actuate themselves by the energy from chemical reactions. The chemical propulsion is suitable for a wide variety of micro- and nanorobots with different shapes [132] which can meet the needs of various application scenarios. For example, researchers have developed common particles [133–135], nanowires [136,137], microgrippers [138,139], tubular rocket-like structures [140–144], Janus micromotors [145], microbeads with oxide arms [146], asymmetric Pt [147], nanorods [148], different biomolecules [146,149], and combined architectures such as a combination of a biomolecule and a nanorod [146]. Different shapes of micro- and nanorobots have different characteristics. Particles and nanorods allow straightforward surface modification. Tubular motors can have a larger driving force and faster propulsion speed. Microgripping devices are capable of grasping and releasing objects. The Pt nanorobot, which has an asymmetric structure, maintains a stable rotational motion rather than arbitrary and uncertain movement. In other words, an asymmetric structure is designed to create a local gradient (e.g., chemical, acoustic, or thermal) [150]. Some nanorobots do not perform their tasks independently; to complete a certain task, hundreds of robots cooperate. To realize this concept, scientists have studied swarms of micro/nanomotors. For instance, inspired by animal interactions, Kagan et al. [134] studied the collective behavior of synthetic nanomaterials. Unlike light-driven diffusiophoretic swarming, chemically induced swarming was the first to rely on intact, monocomponent Au MPs to catalyze redox reactions instead of particle degradation into ions and radicals. Xu et al. [151] also showed the controlled swarm movement of synthetic nanomotors and separation of different nanomotors. This effect relies on the interaction between the individual nanomotors and the pressure gradients generated by the acoustic field, which triggers rapid migration and assembly around the nearest pressure node. A swarming mechanism was proposed. The assembly process is reversible, and the movement of the swarm can be controlled by changing the frequency of the acoustic field. Any other chemically driven micro- and nanorobots that convert chemical energy into mechanical work rely on different principles. For example, some micro- and nanorobots are propelled by generating local gradients of concentration through a surface reaction

[133,150] or pressure gradients [151]. Micro- and nanorobots also exist that propel themselves by generating an electrical potential [133]. These robots can generate autonomous motion by the localized electrolyte gradient [134]. In addition, enzyme molecules can propel themselves by harnessing the energy released during enzymatic reactions, termed enzyme-based micro/nanomotors [149]. A micromotor was developed that uses Pt nanoparticle-DNA conjugate as a motion-inducing catalyst, producing a motion signal only in the presence of the DNA target [135]. In chemical actuation, gas bubbles are generated by chemical reactions, and the use of these bubbles to propel micro- and nanorobots has been studied most extensively [140,141]. Among the gases, oxygen is used most often and is derived from the catalysis of hydrogen peroxide [147,148]. Additionally, carbon dioxide from calcium carbonate [152] and hydrogen from water [145] have been used, eliminating the requirement for the common hydrogen peroxide fuel. To make micro- and nanorobots with excellent performance characteristics, many optimization methods have been implemented, such as the exploration of new fuels with better biological compatibility [137], studies of the effect of different structures on the speed of motion [136,148], modification of the surface by doping and determination of the optimal concentration of dopants [134,153], and control and increase of the speed through various methods such as adjustment of the operating temperature [130]. Furthermore, researchers have focused on decreasing the cost. Teo et al. proposed tubular microrobots propelled by gas bubbles generated by a silver catalyst, which is less expensive than Pt [140]. Gao et al. [142] produced microtube engines by low-cost membrane template electrodeposition. Researchers have also discussed efforts to improve the fuel economy and hence to lower the required fuel consumption [130]. Despite the advances in micro- and nanorobots described above, the use of micro- and nanorobots based on enzymatic reactions for the delivery of drugs in vivo still poses a high risk because it is challenging to determine whether the robots are biologically stable and whether their motion is sufficiently accurate. Another drawback of using chemical reactions to drive micro- and nanorobots is that it is challenging to obtain feedback. Due to the short lifetime of the chemical reaction processes, micro- and nanorobots can move for a short time only.

2.1.3   Biological actuation

To address the actuation of micro- and nanorobots, another strategy is the application of biological motors [154–157]. In other words, in addition to synthetic micro- and nanorobots, biological organisms can be used as components of micro- and nanorobots. The biological organism can act as a driving part of the biohybrid micro- and nanorobot [155,158,159] by combining biology and robotics; alternatively, it can constitute the robot itself [160,161]. These biological organisms integrate their inherent characteristics (which are well beyond the state of the art in engineering, i.e., small size, natural structural advantages, high energy efficiency, high sensitivity and favorable environmental adaptability) into robots that can respond to external stimuli in real time, which can greatly improve their performance. A variety of microorganisms have been used as actuators of micro- and nanorobots. Among these, the most widely used are a variety of flagellated bacteria. For example, Sitti et al. [162,163] used flagellar motors inside the intact cell of S.marcescens bacteria as propeller for a 10 μm polystyrene (PS) bead and achieved on/off motion control of the bead. In further work, this research group designed microswimmers with a higher speed that were made of mostly single Escherichia coli bacteria attached to the surface of drug-loaded polyelectrolyte multilayer (PEM) microparticles with embedded magnetic nanoparticles [164]. Park et al. [165] developed a bacteria-based microrobot with Salmonella typhimurium attached on the surface of a PS microbead. The bacteria used for these robots rely mainly on flagella to convert the ion-motive force into a mechanical force. Other microstructures, liposomes, and fluids all can be driven by flagellated bacteria [161,166,167]. The form of a swarm is typically adopted while using flagellated bacteria as actuators of micro- and nanorobots, such as bacterial carpet [161] and bacteria gathered in the patterned area of the bead [159]. Of course, a single cell can also be used as a robot. For example, the unicellular, biflagellated algae Chlamydomonas reinhardtii (CR) were chosen by the Whiteside's group for transporting microscale loads. CR cells are approximately spherical in shape and have a diameter of 10 μm; two flagella are approximately 12 μm long, similar to a transport microrobot [168]. In addition, the inherent taxis characteristics of bacteria play an important role in the investigation of micro- and nanorobots. Martel [169] combined ferromagnetic materials and magnetotactic bacteria, MC-1 bacterium, to develop a device; in subsequent work, this group then used flagellated magnetotactic bacteria as self-propelled natural microrobots to realize magnetotaxis-based actuation of a swarm [170]. They also proposed a strategy for attaching drug-loaded anoliposomes to MC-1 bacteria to realize the delivery of therapeutic cargo. Furthermore, based on an investigation of the collective chemotaxis behavior of S. marcescens bacteria, Zhuang and Sitti [158] designed biohybrid microswimmers with chemotactic steering capability. A bacterirobot with selectively patterned S. typhimurium developed by Park et al. also showed chemotaxis motility [165]. The phototaxis of CR mentioned above also enabled navigation and control of the cell [168]. Moreover, in addition to bacteria and algae cells, mammalian cells have been used for the design of microengines. Typically, mammalian contractile cells are combined with flexible materials to drive

soft micro- and nanorobots [171]. For example, contractile muscle cells such as cardiomyocytes can be integrated with micromechanical structures, generating structural bending or deformation to produce motion [172]. Spermatozoa are a kind of reproductive cell with a long flagellum that can provide actuation for forward motion. Spermatozoa are adapted to move in viscous fluids and hold considerable promise for serving as carriers in the biomedical field. Therefore, the sperm cell itself has been investigated, and its application to robotics has been studied [173,174]. Magdanz et al. [60] focused on research into spermbots. They designed a micro-bio-robot comprising a motile sperm cell and a magnetic microtube. The robot relies on the flagellar of the cell to move. A magnetic microtube consisting of rolled-up thin films provides a cavity to trap the cell, allowing the motion of a single sperm cell to be directed with an external magnet. They then focused on improving the spermbot performance and proposed several methods, including reducing the length of microtubes, functionalizing the inner surface of the microtube and adding caffeine, to boost the speed [175]. Furthermore, the research group of Qian created a DNA molecular robot to perform complex nano tasks such as "sorting". The DNA robot was a single-stranded structure consisting of 53 nucleotides with one leg and two foot domains for walking and one arm and one hand domain for picking up and dropping off cargo; the robot was approximately 20 nanometers tall. DNA robots and DNA piles form double strands based on the nucleotide-base pairing principle of nucleotides, enabling the DNA robots to walk without any energy supply [160]. The most prominent advantage of biomaterials is their excellent biocompatibility. However, if the composition of the hybrid micro- and nanorobot includes living organisms and if it is desired for the robots to have long-term mobility, it is necessary to create living environments that are suitable to prolong life. For example, their application environment may be limited to liquids that contain the nutrients needed by living organisms. Additionally, the supply of required gases may be necessary; thus, the operational environment of such robots must be free flowing.

2.1.4 Hybrid actuation

In the previous section, we reviewed micro- and nanorobots driven by various methods, including magnetic and electric fields, light, temperature, acoustic, piezoelectric effects, and chemical and biological materials. However, there are some micro- and nanorobots that do not rely solely on one type of actuation methods to achieve motion. Rather, they use a combination of the abovementioned drive modes. Hybrid actuation of micro- and nanorobots has thus been a major topic of research. Magnetic actuation constitutes a large proportion of the actuation approaches used for the micro- and nanorobots, and hybrid actuation methods combined with magnetic actuation have also aroused the interest of

many researchers. Park et al. [176] proposed a hybrid actuated microrobot predominantly actuated by an electromagnetic field to overcome the flow of the bloodstream in large blood vessel and actuated by the bacterial chemotactic response and self-motility in the small blood vessels. That is, different driving methods can be adopted in different application scenarios. Furthermore, the research team led by Professor Martel successfully developed a nanorobot based on magnetic/oxygenotrophic bacteria. With the guidance of an external magnetic field and the bacteria's perception of hypoxic regions, this nanorobot can effectively carry drugs to the depth of a tumor and to anoxic areas. The movement of the bacteria combines the guidance of external magnetic fields, the self-propagation of bacteria, and the bacteria's perception of anoxic regions [59]. Hybrid actuation can combine the advantages of various actuation methods while avoiding their disadvantages. For example, Gao et al. [177] proposed a synthetic hybrid nanomotor combining chemically powered propulsion and magnetically driven locomotion that consists of a flexible multisegment Pt-Au-Agflex-Ni nanowire, with the Pt-Au and Au-Agflex-Ni portions responsible for the catalytic and magnetic propulsion modes, respectively. The nanomotor can rapidly and conveniently switch from the catalytic to the magnetic mode, which can address the fuel depletion and salt limitation issues common to chemically powered motors by switching to magnetic propulsion. Furthermore, soft microrobots exist that are actuated by a magnetic field and capable of responding to pH [178]. The magnetic field can also be combined with piezoelectric [179], acoustic [180,181], optical [182,183], and other methods for the drive of micro- and nanorobots. Furthermore, the driving force generated by the combination of chemical and other methods (i.e., acoustic, light, etc.) can be used for micro- and nanorobots [184,185]. Additionally, the thermoelectric effect has been used in the research on the actuation of micro- and nanorobots [186], such as in the realization of an electrothermally activated microgripper [187,188]. A steerable locomotive device as small as 30 μm that uses the inertial impact drive as the thrust method combines thermal actuation [189]. The adoption of the hybrid drive method takes advantage of other single drive methods and circumvents their shortcomings. On the one hand, the hybrid driving method can improve the performance of the micro- and nanorobots and enable more diverse functions. On the other hand, the hybrid driving method often requires the imposition of more external conditions on the micro- and nanorobot and increases the complexity of the control method.

2.2 Design strategies

The design strategy is an important topic in the investigation of micro- and nanorobots. Significant efforts have been made

to design different types of micro- and nanorobots to meet different needs. Generally speaking, the design of micro- and nanorobots is inspired by modeling mechanical structures, bionics and bio-syncretic designs. However, regardless of the design strategy adopted, the design of micro- and nanorobots stems from the following considerations: by strategically combining functional elements and molecules and controlling geometric shapes, the robots can fully achieve superior application-oriented structural and functional properties.

Reducing the size of the macroscale mechanical structure to the micrometer or nanometer scale produces micro/nanomachines. Alternatively, it can be stated that the functions that such micro- and nanorobots can carry out are similar to those of the corresponding macroscopic physical objects. For example, taking the macroscopic motor as a prototype, a variety of nanoscale motors have been derived. At the molecular level, Schalley et al. [190] proposed rotaxane-based molecular motors; here, the natural system prototypically shows all the features of a macroscopic motor. Lubrich et al. [191] presented a simple rotational DNA nanomotor (RDM) constructed from an asymmetric DNA rotor and a DNA axle and held in place between a surface and a magnetic bead. The rotor DNA can be continuously rotated under magnetic field control. Using inorganic nanoscale components, Kim et al. [192] assembled an ordered array of nanomotors. More specifically, these nanomotors used nanowires as rotors, patterned nanomagnets as bearings and quadrupole microelectrodes as stators and can be continuously rotated for 15 h over 240,000 cycles. However, it must be admitted that researchers have been more focused on the study of the motors used to transport cargo or detect substances, similar to macroscale moving vans or sensors, respectively [193,194]. The nanoscale dimensions of these rod-shaped and wire-shaped nanomotors allow them to move autonomously outside cells [148,195] and move to a specific location with subcellular resolution [15,115]. Moreover, nanorotors formed by molecules, nanorods, nanowires and nanotubes have been developed [196–198]. By mimicking the shapes of macroscopic objects, researchers have designed micro- and nanorobots of different shapes, such as corkscrew, gears, scissors, ratchets, shuttles, turnstiles, elevators, cars, and nano/microvehicles [29,99,199–210]. In addition to the appropriate shapes, the designed robots exhibit the corresponding features. For example, the movement of the nanocar is a new type of fullerene-based wheel-like rolling motion that does not involve stick−slip or sliding translation [99]. Mechanical devices based on molecules or nanocomponents can assist in the transport of microscale and nanoscale objects and in the exploration of microscopic or nanoscopic signal transduction, which has great prospects for application in the biomedical field.

A natural system is often able to provide an organism as a reference system that has the most reasonable structure and high performance. A common design strategy for micro- and nanorobots is biomimetics, which describes the mimicry of biology or nature [211]. The use of bionics in the research of various types of robots has achieved remarkable results [212,213]. Here, we introduce the design concepts of bionics in micro- and nanorobot investigation. Many micro- and nanorobots are used to navigate in viscous fluidic environments for biomedical applications. Microorganisms with flagella such as bacteria and many eukaryotic cells are capable of propelling themselves to swim. Based on this capability, researchers have investigated a variety of bionic swimmers [199,214]. These helical microswimmers can even be made from soft materials and have reconfigurable shape, showing desirable propulsive performance at low Reynolds numbers [52,215,216]. Inspired by cilia, Sing et al. [217] designed a collection of self-assembled colloidal rotors that "walk" along surfaces in the presence of a rotating magnetic field. Microrobots with cilia were also developed to mimic cilia-based microorganisms such as the paramecium [218]. Furthermore, the gecko-inspired micro/nanoadhesive foot-hair array has been studied to support the weight of gecko-like robots [219]. A microrobot with a two-way linear actuator using a shape memory alloy (SMA) spring and silicone bellows can generate earthworm-like locomotive motion [220]. Additionally, insects that exist in nature, such as inchworms, locusts, Sirex noctilio, and beetles, all provide inspiration for the design of micro- and nanorobots [221–224]. Imitating birds, researchers have designed a microscale aerial vehicle [225]. Mimicking the structure of fish [226–229] or jellyfish [230–232], researchers have designed microrobots for underwater applications. Besides, Li et al. [233] developed a nanoscale fish-like robot using multiple flexible joints consisting of a gold head, two magnetic body segments made of Ni, and one gold segment as the caudal fin. In addition to animals, plants can also provide design ideas. For example, based on stomatal transpiration in plants, a micropump with features such as high and adjustable flow rates, simple structure and low fabrication cost was developed [234]. As described above, researchers typically imitate macroscopic organisms, and the smallest such organisms are extracellular structures. However, some subcellular substances can also be used for reference. Kinesin and dynein motors, for example, can transport cargo in living cells by walking along the microtubules [235]. Inspired by such biological machines, a synthetic motor based on RNA-cleaving DNA enzymes was proposed for the transport of nanoparticles. In some cases, researchers have not imitated the appearance of the macroscopic devices but rather have focused on imitating their functions. For example, researchers have used original materials to create hands for picking up and releasing goods and to create legs for walking [160,236]. Notably, the designed micro- and nanorobots have both the shape and function of

the prototypes. For instance, microgrippers were designed to mimic the shape of human hands and the ability to grasp objects. From in vitro biopsy to the capture of individual cells, the size of microgrippers is continuously decreasing, while their accuracy is increasing [103,237,238]. Although the performance of micro- and nanorobots designed by bionics is still far behind that of biological systems, it cannot be denied that nature provides inspiration to researchers. Moreover, as technology advances, the performance gap between robots and bionic prototypes is expected to decrease.

Biohybrid robots or bio-syncretic robots are a new type of robots that can be developed by merging electromechanical systems and biological materials with desirable functions to integrate the advantages of both living biological materials and non-living systems. In recent years, research on these kinds of robots has attracted wide interest [239–241]. In particular, the publication trend on biohybrid actuation shows that the development of biohybrid actuation is significantly fast in recent years [242]. Research on biosynthetic micro- and nanorobots has also made significant progress [155,239,243]. Biohybrid micro- and nanorobots typically consist of two main components: living biological cells acting as drivers and scaffolds for supporting the cells. The biological components of these bioinorganic hybrid micro- and nanorobots are typically muscle cells, flagellated bacteria or cells and rotary proteins. Muscle bundles often provide power to micro- and nanorobots [172,244]. Among the many muscle cells, cardio myocytes have spontaneous contractile properties and are most commonly used as actuators for micro- and nanorobots. For example, the combination of a PDMS microchip with a cultured pulsating cardiomyocyte sheet can form a cell micropump system, and cell-based fluid movement in the microchannel can be activated by actuating the diaphragm [245]. That group also developed a bio-microactuator consisting of a sheet of PDMS embedded with an array of micropillars and primary neonatal rat cardiomyocytes [246]. The driving force of cardiomyocytes is remarkable. Williams et al. [247] designed a swimmer consisting of a polydimethylsiloxane filament with a short, rigid head and a long, slender tail. The cardiomyocytes are selectively cultured on the tail to propel the swimmer. That group increased the speed from 5–10 μm s^{-1} to 81 μm s^{-1} by adding a tail. Additionally, skeletal muscles contract after being stimulated and are typically used in the design of biohybrid robots under electrical stimulation or under optogenetics engineering. However, the sizes of the robots currently researched are mostly beyond the micro/nano size [248,249]. To supplement this research, it is necessary to reduce the size of these robots to the microscale or nanoscale. Additionally, flagellated cells or bacteria can be used in the design of biohybrid micro- and nanorobots [250,251]. Schmidt et al. proposed two types of microrobots;

the first was the combination of a sperm and a microtubule for mobility, and the second was the combination of a sperm with a helical structure. Tubular and helical spermbots have been used for motile and immotile sperm guidance and transport, respectively [60,252]. In another approach, the combination of an engineered substrate, an Fl-ATPase biomolecular motor and fabricated nanopropellers composed a nanorobot, the motion of which was driven by adenosine triphosphate and stopped by sodium azide. The biological components of the biohybrid micro- and nanorobots are often used as robotic engines to drive non-biological components. Biohybrid robots that use flagellar cells or bacteria as the engine typically have smaller dimensions, whereas biohybrid robots that use muscle cells as the engine typically have larger sizes that can reach even the millimeter level. Biohybrid micro- and nanorobots offer advantages such as untethered operation, high sensitivity, and high energy efficiency. However, one of the great challenges in using biocomponents is maintaining the viability of biological components. Otherwise, the robots soon lose their function.

2.3 Fabrication techniques

The processing of conventional robots typically depends on tools such as CNC machines, but when the scale of the robot is reduced from the macroscale to the microscale or even the nanoscale, these conventional processing methods are no longer applicable. Therefore, it is necessary to develop new fabrication methods for micro- and nanorobots. The manufacture and assembly of such robots has thus become an important branch of this research field [117,213,253]. We therefore review the main approaches for the fabrication of micro- and nanorobots, involving lithography, material deposition, material assembly and other methods.

As an unconventional 3D printing method, photolithography is often used for the fabrication of micro- and nanorobots [254]. Using lithography technology, Horiguchi et al. [255] fabricated a microcasting mold and then cultured reconstructed cardiac tissue in the mold to form a bioactuated microdevice. Briefly, the photolithography process mentioned here consists of using ultraviolet light to cure photoresist through a mask. Yang et al. [256] developed a system that can achieve optofluidic maskless lithography. In contrast to other techniques using a physical mask, projection light can be dynamically modulated by a digital micromirror device (DMD). The mask can be changed in real time to meet the requirement of high-throughput fabrication. In addition, another 3D laser lithography method can more precisely control the geometry of the target sample and can make a porous structure that can be used as a biological scaffold [257]. This lithography technique uses the elliptical spot formed by two lasers as the processing tool. Local exposure of the photoresist is achieved by controlling the

movement of the sample platform. When removing the un-exposed photoresist in a developer, a 3D porous microrobot is produced that can be used for transport. In the work of Nelson et al. [258, 259], porous micro- and nanostructures were also developed through lithography, which could be more useful than non-porous micro- and nanostructures for targeted drug delivery and release, and the capabilities of such micro- and nanostructures as cargo transporters had been demonstrated by loading their pores with dyes and hydrogels. Additionally, microstereolithography is a new type of microfabrication technology developed on the basis of stereolithography (SL). Relative to the conventional SL process, microstereolithography uses a smaller laser spot (a few micrometers) so that the photoresist undergoes a photo-curing reaction in a very small area [260]. Most currently used microstereolithography processes are limited to the use of a single material, whereas many applications (such as tissue engineering, biological organs, and composites) require micro/nanostructures of multiple materials. Choi et al. [261] developed surface projection microstereolithography based on a syringe pump to achieve multi-material micro/ nanoscale 3D printing, and the syringe pump was integrated into an existing microstereolithography system for the transport and distribution of various materials. That group also developed multi-material (three different resin materials) microstructured 3D printing using the developed devices and processes. The combination of microstereolithography and surface biomimetic modification can produce a scaffold with better biocompatibility and improve the performance of the scaffold in bone tissue engineering [262]. Lithography can create complex miniature objects with a realistic 3D shape; with the growing demand, however, smaller dimensions and higher precision are still the direction of development.

Another common method for the fabrication of micro- and nanorobots is material deposition. Physical vapor deposition is often used. Conventional physical vapor deposition typically deposits metal in a part of a micro- and nanorobot that has been molded to promote driving, assist navigation, or increase adhesion. For example, Gao et al. [263] designed plant-based bioinspired microswimmers by creating a large array of helical vessels and depositing thin layers of Ti and Ni sequentially on the long spiral vessels to improve adhesion and magnetic actuation, respectively. Wang et al. [264] designed an electrochemically grown Au-Ru microrod with sequentially deposited $Cr/SiO_2/Cr$, Au, and Pt layers. Here, the second Au/Pt catalytic bilayer added a perpendicular force that moves the rod toward the center of the orbit induced by the asymmetric flow. Furthermore, glancing-angle deposition is a special physical vapor deposition that is typically used to break the symmetry of the deposit sediment [265,266]. He et al. [266] fabricated L-shaped Si/Pt nanorods by glancing-angle deposition, for example. The catalytic

reaction on the surface of the Pt layer generates a propulsion force to push the nanorod from the Pt side. Unlike the vapor phase deposition methods, electrodeposition allows bottom-up filling of the templates with complex shapes. The group of Nelson created hybrid artificial bacterial flagella (h-ABFs) consisting of a ferromagnetic alloy head and a helical polymer tail by template-assisted two-step electrodeposition [267]. That group also designed a hybrid magnetoelectric core–shell composite nanowire with a magnetostrictive core and a piezoelectric shell. In this process, a piezoelectric polymer was first fabricated into nanotube arrays through a template-based wetting technique. In the second step, an alloy with a large magnetostrictive coefficient was electrodeposited inside the tubes to form the core–shell nanowire [12].

Material assembly also plays an important role in the assembly of micro- and nanorobots. The intuitive concept of material assembly is to assemble the components of the micro- and nanorobot into the ideal shape while achieving the ideal function. Different inorganic materials or biological and non-biological materials can be assembled regardless of the kind of material used as the actuator; alternatively, living organisms can be directly assembled [161,268–270]. Exploiting different principles, micro- and nanorobots can be manufactured through self-assembly. For instance, a tubular or helical micro/nanostructure can often be obtained with a self-scrolling or self-rolling technique [271–274]. The self-assembly process typically involves the assembly of 2D templates into a 3D structure [275]. In addition to inorganic materials, biomaterials can be self-assembled [172]. Furthermore, layer-by-layer electrostatic self-assembly is a common method for machining micro- and nanorobots. This method makes full use of the oppositely charged polyelectrolyte [276]. With the template-assisted layer-by-layer assembly, micro- and nanorobots are generally shaped like rods or tubes [277–279].

However, with the increase of the number of functions and improvement of performance, the structure of micro- and nanorobots is expected to be relatively complex, and a single assembly method is unlikely to meet the requirements. Therefore, the assembly of micro- and nanorobots with complex structures is typically realized by combining different manufacturing methods [280]. For example, microtubes and magnetosperm can be fabricated by photolithography and electron beam evaporation techniques [60,281], while helical micromachines such as capsules and syringes can be manufactured using 3-D direct laser writing (DLW) and physical vapor deposition techniques.

In addition to the abovementioned fabrication techniques, many other techniques can be used to fabricate micro- and nanorobots, such as micromolding, focused ion beams, and template-based wetting techniques [12,282,283]. Different assembly technologies have different characteristics. For

example, layer-by-layer assembly increases the maximum load of micro/nanostructures but reduces the speed of these structures.

2.4　Motion control

Another problem faced by an assembled, shaped micro- and nanorobot is motion control. In simple terms, motion control is to control the position and speed of the micro- and nanorobot in real time so that it moves according to the expected trajectory and keeps the motion parameters within the set range. In the previous part of this article, the different actuation methods of micro- and nanorobots have been reviewed. The control of a micro- and nanorobot's motion and the actuation methods are closely related. For example, Hong et al. [284] used chemotaxis and phototaxis to achieve global directionality control in artificial micro/nanomotors while maintaining local randomness, suggesting the interaction between the powering mechanism and the directing method. Zhou et al. [285] designed a micromotor driven and controlled by the visible light. The motion of the micromotor can be quickly started and stopped by switching the light on and off and the velocity can be modulated by controlling the light intensity; In their subsequent work [286], external magnetic field was applied to guide the micromotor.

Magnetic driving is the most widely used driving method. Researchers typically use magnetism to control the motion of micro- and nanorobots regardless of how the robot is driven. For example, both acoustically propelled nanowire motors [287] and chemically powered Janus microsphere vehicles [288] can be steered by magnetic fields. In addition, motion control of micro- and nanorobots often uses time-varying magnetic fields. Kim et al. [289] artificially induced the magnetization of Tetrahymena pyriformis by magnetizing integrated iron oxide particles; the direction of travel of the single cell was then controlled by an external time-varying magnetic field. Time-varying magnetic fields can make micro- and nanorobots execute customized movements. A controllable stick–slip motion across the surface of a microrobot was achieved by using time-varying magnetic fields [290]. When the magnetic field is used to control the motion of the micro- and nanorobot, the adjustment of the parameters of the magnetic field is relatively important. For example, in the work of Nelson et al. [52], to generate a steerable corkscrew motion for helical micromachines, the input frequency of the rotating field had to be increased, and when the applied field strength was increased, the applied frequency also had to be increased to induce a corkscrew motion. By choosing appropriate values for magnitude, direction, and frequency of the magnetic field, individuals and subgroups of magnetic microrobots can be selected and translated [291,292].

In addition to magnetic fields, micro- and nanorobots

driven by chemical reactions can achieve speed and direction control through the concentration and distribution of the chemical fuels. Optimization of the fuel and surfactant concentrations can increase the speed of the microbots [293]. Catalytic motors are relatively sensitive to the gradient of the fuel imposed in the system [294], and Pt-Au rods are used to travel toward locations with high fuel concentrations [295]. In addition, the introduction of some substances accelerates the movement of micro- and nanorobots [194, 296]. The micro- and nanorobot's motion control method is not limited to this approach. Additionally, the motion direction of chemically propelled bimetallic Au-Ru microrods can be reversed by US [297]. The average velocity of a self-propelled conical tubular micromotor can be adjusted through the design of the semi-cone angle [298]. Even the nanorobot made only of Pt can steer or navigate by exploiting its finely designed geometry [147].

Micro- and nanorobots are mainly oriented to biomedical applications; consequently, real-time positioning of micro- and nanorobots is particularly important. The feedback control of existing micro- and nanorobots is generally based on vision [287,288,299] and force feedback [300]. Li et al. [288] designed a closed-loop control system based on visual feedback for microvehicles. Real-time visual feedback was provided by the micro-scope-coupled CCD camera. In their work, they introduced artificial intelligence (AI) into the control of microrobots, which provides a new approach to manipulating the micro-structure. The smart microrobot can identify target objects in time, such as identifying cancer cells and normal red blood cells, and autonomously select the best path to track cancer cells.

Although some studies have already shown intelligent control of micro- and nanorobots, the low level of intelligence is still a common problem in the study of micro- and nanorobot motion control. In the existing research, most of the micro- and nanorobot control has remained two-dimensional. Nevertheless, Sitti et al. [301] achieved independent control of multiple magnetic microrobots in three dimensions, and Nelson et al. [52] designed their helical micromachines to transport cargo in three dimensions. Overall, however, there have been few studies on the three-dimensional motion of micro- and nanorobots. Therefore, the realization of high-precision, quickly responsive, and intelligent three-dimensional motion of micro- and nanorobots remains a research direction for future exploration.

3　Challenges in the development of micro- and nanorobots

With the development of micro/nano technology, robotics, biomedicine, and electromechanical science, research on micro- and nanorobots has made considerable progress.

Previous research has achieved the movement and control of micro- and nanorobots and explored their promising applications in the biomedical field. However, to accommodate the ever-increasing actual demand, some challenges associated with micro- and nanorobots must be addressed by follow-up research.

First, micro- and nanorobots should be multifunctional. Constrained by the micro/nano size, existing micro- and nanorobots have a single function, and it is challenging to integrate multiple functions (i.e., actuation, perception, assessment, and intelligence) into one robot. In practical applications, it is important for intelligent micro- and nanorobots to incorporate signal perception, acquisition, processing and transmission. An improved feedback mechanism is also necessary to grasp the real-time position of the robot and the results of treatment of a lesion, for example, preventing the micro- and nanorobot from losing contact with external controls.

Second, micro- and nanorobots should solve the problems encountered in clinical applications and cross the gap between scientific research results and market demand, and one of grand challenges is to realize micro- and nanorobotics devices for the clinical application [302]. Regarding micro- and nanorobots for medical services, although a variety of prototypes of micro- and nanorobots have been developed, they are rarely used yet in clinical applications. Application efforts regarding micro- and nanorobots in vivo should consider the biocompatibility, reliability and biodegradability. The micro- and nanorobots that enter the living body should replicate immunization safety; that is, they should not be rejected by the body, should be harmless to normal tissues, and should have no side effects. The ability to pass through barriers such as blood vessel walls and biological tissues is also required. In addition, the robot's material should be biodegradable, i.e., no residue should remain in the body after the task is completed. Otherwise, the robot must be equipped with an integrated recycling mechanism. Only by solving these problems can micro- and nanorobots move from the laboratory to the clinic and the market.

Third, micro- and nanorobots need new energy conversion mechanisms, more robust wireless drive and control methods, and more reasonable fabrication technologies. The existing driving methods have drawbacks in all these areas. For example, the magnetic drive requires the use of an external magnetic field, the electric field drive requires external electrodes, and the light drive needs light to penetrate the tissue. Furthermore, the majority of existing methods control the micro- and nanorobots to move in the 2D plane and lack the potential for movement control in the third dimension. Regarding the energy supply, many micro- and nanorobots are driven by corrosive chemical fuels, raising obstacles to the use of robots in vivo. Unlike the in vitro environment, in vivo applications require micro- and nanorobots to travel longer distances to the specified location with accuracy at the micro/nano level. Therefore, the robot should have greater propulsion capability and higher speed to improve efficiency. For better diagnosis and treatment, the robot should be better able to load more drugs. For commercialization, a reduction of manufacturing costs should also be considered. Research is now being conducted to use low-priced metals instead of expensive metals [140] or to use water instead of other chemical reagents [145] to drive micro- and nanorobots.

Fourth, micro- and nanorobots need innovative materials. Bio-syncretic robots have the advantages of both living components and nonliving components [303] and the bio-syncretic micro- and nanorobot has been an important part of the micro- and nanorobots field. Moreover, some living microorganisms can be directly used to assemble micro- and nanorobots. Living organisms can act as sensing or driving elements for these types of robots. Relative to inorganic materials, biomaterials have advantages such as higher sensitivity. However, once such robots are used in the air, the long-term survival of living biological components is a challenge. Micro- and nanorobots must be supplied with nutrients and gases and operated in a controlled-humidity environment. Therefore, some innovative materials with better environmental adaptability should be investigated.

Finally, precise cluster control of micro- and nanorobots deserves further study. Faced with complex tasks, a single micro- and nanorobot cannot be in two places at once. At this point, clusters of micro- and nanorobots can complete tasks through collaborative cooperation. How to implement synchronous or independent control of the micro- and nanorobots in the cluster is therefore another important research direction. The ideal cluster control strategy should involve the clear division of labor of individual robots within the cluster and information exchange between the robots so that all robots work together in an orderly manner to finish the task. Clearly, the achievement of this goal will require much research effort.

4   Conclusion

Micro- and nanorobot is an important branch of robotics research. Research efforts in the field of micro- and nanorobotics play an important role in the development of these robots. Relative to macroscopic robots, micro- and nanorobots can perform tasks on a very small scale. Additionally, micro- and nanorobots have small sizes, low weight, and large thrust-to-weight ratio. Micro- and nanorobots can also accurately navigate in complex environments with high flexibility, high sensitivity, and high precision. With these advantages, micro- and nanorobots are widely used in fields such as biosensing, disease diagnosis and treatment, drug delivery, and minimally invasive surgery. Micro- and na-

norobots are the products of multi-disciplinary integration. Research in this area drives the common progress of multiple disciplines, such as robotics, mechanical electronics, materials science, bionics, and biomedicine, and shows favorable prospects for further development. This review describes selected related research on the actuation, design, fabrication, and motion control of micro- and nanorobots. The research progress of micro- and nanorobots and the challenges that may be encountered in the future are also discussed. Although existing micro- and nanorobots have the problems of single function, challenges in integration, and non-intelligence, the continuous advancement of science and technology is promising for exploring opportunities and overcoming these challenges. In the future, micro- and nanorobots may be made from smart materials and manufactured with advanced fabrication techniques. They may also have multiple features, such as multi-functionality, reconfigurability, intelligence, and feedback, and have self-evolving, self-healing, and self-replication capabilities. In addition, biohybrid micro- and nanorobots may become widely used because they offer the advantages of both living biological materials and inorganic materials.

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