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REVIEW

Recent progress on the design and fabrication of micromotors and their biomedical applications

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Abstract

The advancement in the micro-/nanofabrication techniques has greatly facilitated the development of micromotors. A variety of micromotors have been invented with powerful functions, which have attracted a broad range of interests from chemistry, physics, mechanics, biology and medicine. In this paper, we reviewed recent progress in micromotors and highlighted representative works. The mechanisms of micromotors by internal and external energy sources were described. We described general fabrication strategies of the popular micromotors (wire, tubular, helical and Janus) including bottom-up and top-down approaches. In the application section, we primarily focused on the biological applications, such as biological cargo delivery, biosensing and surgery. At last, we discussed the current challenges and provided future prospects.

Keywords Micromotor · Nanomotor · Electric tweezers · Drug delivery · Nanorobot · Micromachine

Introduction

Micromotors, also called micromachines, are micrometer-scale moveable entities. They can easily enter human body, which were only appearing in scientific fiction films and imaginations decades ago. Today, with the fast development of micro-/nanofabrication techniques driven by the matured semiconductor industry, as well as the advancement of nanoscience, the fabrication of micromotors has been much easier. Micromotors powered by different mechanisms were developed, ranging from electric, magnetic, optic, acoustic and chemical reactions. Being able to freely move in vivo or in vitro is the basic function of the micromotors, and it is also the foundation toward more complicated missions, such as cargo (e.g., drug, DNA, cell) delivery, cell isolation and surgery.

The inspiring progress in the field of micromotors in the past decade, though still is in its infant stage, has greatly encouraged further explorations to bring the dream of nanorobots into the reality. Tables 1 and 2 highlight early prototypes of micromotors and recent progress. Micromotors can be powered by chemical energy and external fields. Micromotors could be a micro/nanostructure modified with various functions or as a sole component integrated into a micro/nanodevice. Precedent efforts scaled down motors from centimeter level [1] to micrometer level [2], and recently to the nanometer level [3]. The advances in materials science and nanoscience keep pushing the limit of the degree of miniaturization and functionality.

One early example was classical self-propelled micromotors powered by chemical energy. This type relies on the catalytic chemical reactions to generate bubbles in liquid to drive the movement of the catalytic particles. Such micromotors are primarily made of catalytic materials such as Pt and Ag [2, 4–7], while their motions are random and non-directional due to lack of direction control. Recently, Janus-like nanoparticles, with only one side, were made of catalytic materials, were developed to provide certain degree of directional control [8, 9].

The miniaturized "biological micromotors" are often seen in the nature with complicacy and functionality that the man-made device can hardly compare. As a result, the design of man-made micromotors can be inspired from nature. For example, bacteria flagella are nature's effective solution to swim at low *Re* number [10]. It inspired the advent of artificial

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Table 1 Representative early works of micromotors (before 2012)

Types	Materials	Power [P] Direction [D]	Main fabrication methods	Biological applications	Refs.	Year
Biomolecules	F_1-ATPase	[P] ATP	Recombinant	N/A	[45]	2000
Wire[a]	Pt–Au	[P] Catalytic	Template-assisted electrodeposition	N/A	[2]	2004
Helical	SiO_2	[P] [D] Magnetic	GLAD[b]	N/A	[27]	2009
Gripper	Cr/Cu/Ni/Au	[P] [D] Catalytic	Photolithography	Cell Manipulation	[79]	
Helical	Metal	[P] [D] Magnetic	Photolithography	transportation	[11]	
Wire	Metal	[P] Catalytic [D] Magnetic	Template-assisted electrodeposition	Drug delivery	[4]	2010
	Au	[P] [D] Electric	Photolithography	Drug delivery	[16]	
Tube	Ti/Fe/Pt	[P] Catalytic [D] Magnetic	Roll-up method	Manipulated cell	[17]	2011
Janus	SiO_2/Co–Pt(Pd)	[P] Catalytic [D] Magnetic	Self-assembly evaporation	Transported cargo	[8]	
Wire	Metal	[P] [D] Acoustic	Template-assisted electrodeposition	N/A	[87]	

[a]Here we defined wire as both wire and rod shape for simplicity
[b]Glancing angle deposition

Table 2 Representative recent works of micromotors (after 2012)

Types	Materials	Powering [P] Direction [D]	Fabrication methods	Biological applications	Refs.	Year
Janus Particles	SiO_2/Cr/Pt	[P] Pt catalyzing H_2O_2	Template Evaporation	Intracellular delivery of DOX[a]	[35]	2014
Janus Particles	SiO_2/GO[b]	[P] Glucose or H_2O_2 catalysis	Wet chemistry	N/A	[44]	2015
Wire	Zn/PEDOT[c]	[P] Zinc-H^+ reaction	Template-assisted synthesis	Drug delivery	[76]	2015
Tube	SiO_2/Urease	[P] Urea catalysis	Template-assisted synthesis	N/A	[46]	2016
Helical Swimmer	Polymer/Ni/Ti	[P] [D] Magnetic field	3D laser lithography	Cell capture and transport	[81]	2016
Needle	Ca Oxalate $CaCO_3$/Fe/Ti	[P] [D] Magnetic field	Plants	Intracellular delivery	[84]	2016
Tubular Tetrapods	Polymer/Fe/Ti	[P] Sperm [D] Magnetic field	3D laser lithography	Drug delivery	[12]	2018

[a]Doxorubicin
[b]Glucose oxidase
[c]Poly(3,4-ethylenedioxythiophene)

bacterial flagella powered by magnetic field [11]. Sperm is another well-recognized motile biomolecule that can self-propel using the energy from adenosine triphosphate (ATP). Sperm can be integrated into a micro/nanodevice for self-powering [12].

The exploration of different powering mechanisms is one growing trend in this field. The early design of micromotors was mostly based on chemical catalytic reaction to generate self-propelling bubbles. The device usually loads a layer of catalyst on its surface, facilitating the in situ catalytic reaction of the fuel reactant surrounding the device. H_2O_2 initially attracted much attention and now is still a very common fuel. Nonetheless, alternative fuels were also proposed due to the concern of the health risk associated with H_2O_2. Apart from the chemical powering mechanism, the powering based on external fields including magnetic [11, 13, 14], acoustic [15], light and electric field [16] was developed. Notably, the magnetic field was also frequently used as a tool for direction purpose, which assisted the navigation of motor systems powered by other means [17, 18].

With continuing developments of micromotors, their biomedical applications have been largely expanded from the proof-of-concept level of simple "pick, transport and release" to intracellular drug delivery, cell manipulation, biosensor and now evolving to micro/nanosurgery and even to the early stage of in vivo applications (Tables 1 and 2). Herein, we reviewed the design principle, fabrication and biomedical applications of current micromotors; highlight representative works in this field and evaluate their potential for the future nanomedicine; provide reference for researchers from multiple disciplines to understand the science, engineering breakthroughs, promises and challenges in the field of micromotors.

Fundamental physics

The physics of the motion of micromotors is different from that of macroscopic world. Microscopic object in liquid medium suffers from viscosity more significantly than macroscopic object in air. We must carefully consider the relation between the inertia and viscosity. The ratio of inertial force and viscous force to an object is defined as Reynolds number (*Re*):

$$Re = \frac{\rho v l}{\eta}$$

where ρ is density of the fluid. v is velocity of the object with respect to the fluid. l is length of the object. For sphere micro/nanoparticles, l is diameter; for tubing, wire and rod micro/nanodevice, l is length along the direction of propulsion. η is dynamic viscosity of the fluid. Fluid with lower viscosity and greater characteristic length l leads to higher *Re* number, which means the inertia force dominates. A fish swimming in the water is usually a high *Re* situation. In contrast, bacteria swimming in the water are usually a low *Re* situation due to small value of l and v. When an object is at micrometer or nanometer scale, the *Re* is low, and thus for the micromotors, the inertial behavior was nearly negligible.

In a world as small as micromotors, the Brownian motion generates significant influences as well. The randomized molecular collision from the fluid in biological system will greatly influence how the micromotors act. The mass diffusivity D is calculated as:

$$D = \frac{k_B T}{3\pi d \eta}$$

where k_B is Boltzmann's constant, T is the temperature, d is the diameter of the micro/nanoparticle (suppose perfect sphere shape), and η is viscosity of the medium. From the equation, we can get that smaller particle diameter or smaller viscosity can lead to a larger mass diffusivity, thus greater Brownian motion. When the size scale goes down to nanometer level and the biological fluid is relatively low in viscosity, which is the normal case for body fluids, the Brownian motion seriously matters.

The low *Re* motion and significant Brownian motion synergistically made it very complicated to design, control and understand the motion of micromotors in the biological fluid. However, despite little space to mitigate the Brownian motion, the *Re* number can be increased by gaining a greater velocity or prolonging the linear dimension along the direction of propulsion. Thus, stronger propulsion and a design of wire, rod and tubular shape of microscopic devices are usually preferred.

Beyond the design principle, the advancement in micro/nanofabrication has laid another foundation for the progress of micromotors. Without it, the design will be just a sketch. Miniaturizing a structure down to submicron to nanometer scale is greatly challenging due to the stringent requirement of resolution and precision. The general rule is that a stand-free structure is the precondition for the mobility of the micromotors. Although top-down fabrication was widely employed in the semiconductor industry to mass produce micro/nanostructured surfaces, it seems the bottom-up strategy attracted much attention for manufacturing stand-free micromotors. The micromotors often require integrating multiple functions in one device, such as powering, steering, capturing and releasing the cargo. Building it from the bottom gives more space to arbitrarily design the composition and the geometry of the device. The bottom-up strategy could obtain stand-free products without the need of the stripping-off process. Sometimes, top-down and bottom-up approaches were used jointly, depending on the design of the micromotors.

Fabrication methods

Micromotors with different morphologies have been developed, including spheres, wires, needles, tubes and complex structures such as Janus particles, multilayered structures, rolls and more. Their fabrication methods can be categorized into bottom-up and top-down approaches. For the bottom-up assembly primary relaying on the wet chemistry synthesis, such as hydrothermal methods. Bottom-up strategies can be readily scaled up for manufacturing purpose, and the dimensions can be down to sub-100 nm easily; however, the structures are commonly limited to simple geometries such as wires, spheres, cubes, etc. While for the top-down strategy which is commonly used in the semiconductor industry, it can be used to design and fabricate more complex structures at higher cost when comparing to the bottom-up approaches. In the following, we selected several popular geometries of micromotors and describe their fabrication strategies in detail.

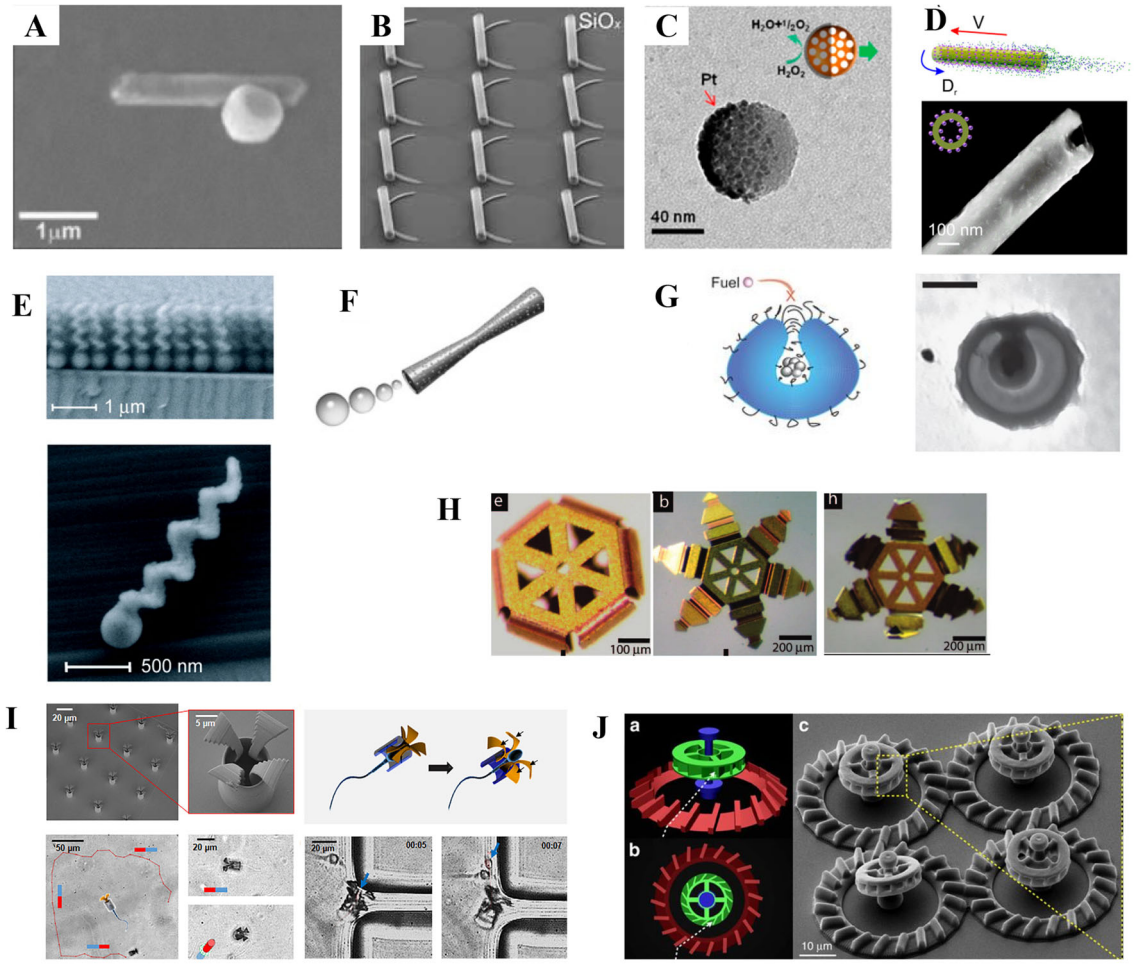

Fig. 1 Different types of micromotors. **a** Scanning electron microscopy (SEM) image of a nanowire motor carrying a polymer particle. Adapted and reprinted from Ref. [4]. **b** The SEM image of SiO/SiO_2 nanotube motor arrays fabricated by rolled-up technique. Adapted and reprinted from Ref. [24]. **c** Janus mesoporous silica micromotors. Adapted and reprinted from Ref. [42]. **d** Silica nanotube motor decorated with urease on both inner surface and outer surface. Adapted and reprinted form the Ref. [46]. **e** Helical SiO_2 swimmers. Adapted and reprinted from the Ref. [27]. **f** Self-propelled tubular micromotors. SiO_2 nanoparticles were loaded in the microtubes. Adapted and reprinted from Ref. [7]. **g** Self-assembled stomatocyte nanomotors. Adapted and reprinted from Ref. [88] **h** Microgripper: it was closed after added the acetic acid, and opened again after added H_2O_2. Adapted and reprinted from the Ref. [80]. **i** Tetrapod micromotors capture and deliver sperms. Adapted and reprinted from the Ref. [12]. **j** Two-photon polymerization method fabricated micromotors for bacteria capturing purpose. Adapted and reprinted from the Ref. [57]

Nanowire micromotors

Maskovits et al. [19] reported a template-assisted method to fabricate metallic nanowires. Electrodeposition was used in combination with porous anodic aluminum oxide (AAO) template. The advantage of this technique is the flexibility to integrate multiple segments of different materials, diameter and length to a single nanowire with excellent control of these parameters, as well as its scale-up potential. For instance, Kagan et al. [4] electrodeposited metals into a porous AAO template, as shown in Fig. 1a. The sequential electrodeposition allows depositing customizable segments, either metals or carbon nanotubes, one after another to form composite nanowires. The Au/Ni/Au/Pt–CNT nanowires and the $Ni/(Ag_{50}/Au_{50})/Ni/Pt$ nanowires were successfully prepared in this way. Another example was completed by Gao and coworkers [5], who used template-assisted electrodeposition to get Ni–Ag nanowire motors. Also, Gradilla et al. [6] also used template-directed electrodeposition to get tri-segmented Au–Ni–Au nanowires motors. Furthermore, Mirkovic et al. [20] explored a more complicated design of nanowires. They fabricated Pt–Ø–Pt flexible nanowire motors. The Pt–Au–Pt was fabricated, and Au was etched away, leaving a hollow region, which enabled the flexible bending of the nanowire. The remaining Pt segments on the two ends were connected by polymer encapsulation.

Then, the flexible wire was stripped off by nitric acid from AAO template. In addition, Sattayasamitsathit et al. [7] utilized AAO template method to fabricate Zn-based nanowire motors, as shown in Fig. 1f. They loaded nanoparticles cargos into a porous membrane template and then electrodeposit zinc into the entire pores. The as-prepared Zn-based micromotors have a biconical geometry.

Microtube micromotors

Template-assisted methods are popular for making tubular micromotor [21]. The silver (Ag) nanowire was used as the template for the sequential electroplating of Pt and Au. After the Ag template was dissolved, the conical nanotube can be obtained. The inner layer of Pt catalyzed H_2O_2 fuel, generating bubbles that flew to the wider opening of the conical canal, thus generating the propulsion. The simplicity of this method made it an attractive option for scaling up the metallic micromotor. For polymer tubular micromotor, recent progress in the rolling up technology offered a viable solution. In 2001, Schmidt et al. [22] reported a strain engineering method to roll up polymer thin film to a nanotube. They later employed this method to the fabrication of tubular micromotors of different materials and tunable diameters [23, 24]. A typical SEM image of an array of rolled-up microtube is shown in Fig. 1b [24, 25].

Another strategy for making tubular micromotors is the layer-by-layer self-assembly method. For example, it was used to make tubular nanorocket [26]. About 18 layers of alternating positively charged chitosan and negatively charged sodium alginate were self-assembled into the inner wall of the porous template, and then the Pt nanoparticles were attached to the inner most surface. The micromotor was obtained after the template was dissolved.

Helical micromotors

Micro/nanoswimmers were designed to have a helical "tail" which mimics bacteria flagella, as shown in Fig. 1e and summarized in Table 1 [27]. They are more geometrically complicated than micro/nanowires, but they can be manufactured via advanced micro/nanofabrications. Ghosh et al. [27] utilized glancing angle deposition (GLAD) to obtain the helical-shaped SiO_2 nanoswimmers on a wafer. The helical swimmers were then stripped off by sonication to become stand free. The GLAD method used in that study originally was proposed by Brett et al. in 2008 [28]. This method combined traditional thin film vacuum deposition and the motion of the substrate. In this technique, substrate was tilted and rotating instead of being held still. At the glancing angle, the materials tend to grow toward the direction of the vapor source, leading to the formation of helical nanostructures. In recent years, the burgeoning direct writing technology also attracted much attention and provided another option for making helical micro/nanoswimmers [29–32]. Three-dimensional direct laser writing can fabricate nanostructures with almost arbitrary shape. For example, Tottori et al. [32] fabricated helical nanoswimmers using 3D direct laser writing. In this fabrication, the photoresist materials (SU-8 or IP-L) were written followed by a development process, which removed the unwritten photoresist. The resulting helical micromotor made of photoresist materials was then coated with magnetic and biocompatible Ni/Ti bilayer using the electron beam evaporation.

Janus micromotors

Janus nanoparticle is a micromotor design distinct from nanowires. They can be fabricated by different approaches. The basic metallic, silica or polymer microspheres and nanoparticles are often commercially available, or at least can be fabricated with well-established means, e.g., the wet chemistry method [29, 30]. Nevertheless, the most critical and challenging step for Janus nanoparticle motor is to generate chemical asymmetry using surface decoration, which allows for unidirectional motion. Physical deposition attracted a lot of attention as a tool to coat nanoparticles. In this technique, a layer of catalytic material can be physically sputtered onto the nanoparticles that are placed on a substrate. Gao et al. [33] sputtered the iridium to half of the SiO_2 nanoparticles to prepare the Janus SiO_2 nanoparticles. The iridium layer can catalyze N_2H_4 fuel to produce N_2, NH_3 and H_2, which propelled the unidirectional motion of the SiO_2 nanoparticles. Guan and coworkers [34] also utilized the sputtering approach to cover a portion of magnesium (Mg) microsphere with platinum (Pt). Less than half of the surface area for each Mg microsphere was immersed into a 2D PVP-film, resulting in asymmetric Pt-covered Mg microspheres. Xuan et al. [35] used similar method, but they used mesoporous silica particles instead and the Pt-covered region constitutes about half of the total surface area of each individual nanoparticle (Table 2).

Micromotors: internal and external powered

The essential difference between the micromotors and other nanostructures is the self-propulsion capability. Self-propelled micromotors present the opportunity to enhance the penetration capability of nanomaterials into body fluids, tissues and cells. The propulsion mechanism of micromotors can be categorized into the internally powered (or self-propelled) and external powered micromotors.

Internally powered micromotors

Bubble propulsion is a major mechanism for chemically powered micromotors. In the bubble propulsion, the bubbles can be generated by the catalysis of the fuel. The most common fuel source is H_2O_2. Micromotors were often modified to have a certain area of catalyst surface, and the in situ catalyst reaction generates H_2 and O_2 bubbles. Chemically powered micromotors based on Pt catalyst were reported [36]. Later, Ni was also investigated as a catalyst [37]. But most studies focused on Pt as catalyst. For example, Pt-catalytic micromotors have been developed in several groups [4, 38–42].

H_2O_2 could be harmful to cells due to the oxidative pressure [43]. Concerned with the unwanted H_2O_2 presence in biological medium, many scholars explored the use of fuel that already exist prevalently or locally in the body, such as glucose [44], ATP [45] and urea [46]. Glucose is a very interesting fuel source in human body, especially when considering its prevalence in the blood and the clinical relevance with diabetes. Schattling et al. [44] developed a submicron-sized Janus particle with hemisphere decorated with enzyme glucose oxidase and catalase. The glucose oxidase enzymatically degraded glucose and produced H_2O_2, which was then decomposed by catalase. This intriguing mechanism avoided the need of prevalent H_2O_2 in the medium. The H_2O_2 was only produced as an intermediate product, thus minimized the amount of it. In this study, the diffusion behavior was found dependent on glucose level. Montemagno's group reported to use ATP as the alternative fuel source instead of H_2O_2 [45]. They developed an integrated device that consisted of a Ni post-substrate, a recombinant F_1-ATPase and a Ni nanopropeller coated with peptide (Fig. 1i) [45]. The rotational motion of the nanopropeller was initiated upon the addition of ATP into the solution. The later explorations of safer fuels by different groups of scientists resulted in various promising options, including urea [46] or water [34, 47, 48] as fuels. As shown in Fig. 1d, The urea-fueled nanorod motor (nanojet) developed in Samuel Sanchez's group [46] avoided the generation of bubbles. The urease was attached to the silica nanotube, and enzymatic decomposition will transform urea into the NH_3 and CO_2 but without forming bubbles. On the other hand, water is perhaps the safest and the most prevalent fuel in the body of living organism, and it has already been used as catalyst for the biodegradation of polymers [49–51] and metals [49, 52]. The water-driven motors were powered by the H_2O reaction with either Mg [34, 47] or aluminum (Al) [48, 49, 52]. Notably, Mg seems to have an acceptable degradation rate in the body for this application, so the pure Mg microsphere was used [48]. But, alloying elements are capable of further tailoring the degradation rate of Mg [53]. Notably, Al was alloyed with gallium (Ga) to prevent the formation of a passivation layer [48].

Chemical gradient in vicinity to the micromotors has also been widely utilized to power the micromotors [54, 55]. Urease enzyme [54, 55] and catalase [55] were powered by the concentration gradient of urea or H_2O_2, respectively, and the gradient was generated by a microfluidic device.

Many progresses in this field were inspired by the nature. Natural substances sometimes function with self-propulsion motility. Motile living organism substances, such as sperm [12, 56], bacterial flagella [57] and ATPase [45], confer the capability of powering a micromotors. For example, Oliver G. Schmidt's team [56] put bull sperms in a microtube. The motility of the bull sperm cells provides a driving force that consumes ATP. The same team also 3D printed tetrapod microstructures (Fig. 1i) that captured individual sperm for powering and drug delivery [12]. The sperm-hybrid micro-bio-motor could be a promising device for delivering drugs or cells. On utilizing the motility of bacteria, individual *E. coli* was captured by a self-assembled 3D microstructure to form a bio-hybrid rotor [57]. The rotor motion was triggered by light, since the *E. coli* strain was gene engineered to be light harvesting.

Externally powered micromotors

External fields such as magnetic, acoustic, optic and electrical fields provide the possibility of fuel-free micromotors for biomedical applications. Optical tweezers have already been demonstrated to be very successful in biomedical applications. [58–60] While in this section, we primarily reviewed magnetic-steered micromotors, and we highlighted promising and fast developing electric-driven micromotors.

Even for chemically powered micromotors, external fields were often applied for the orientation control purpose. Magnetic field can both power and steer micromotors with minimal safety concerns [61]. Wang and coworkers [62] reported the flexible magnetically driven nanowire motors made of Au and Ni. More often, magnetic field was used as a direction tool to assist the chemically powered micromotors. For instance, Solovev et al. [18] reported a rolled-up Ti/Fe/Pt nanotube motor with motions controlled by magnetic field but powered by H_2O_2 decomposition.

Learning from the nature, researchers made further efforts to design and build magnetically driven micromotors with complicated structures. Inspired by bacterial flagella, Bradly J. Nelson and his group [11, 13, 14, 18] developed an artificial bacterial flagella (ABF). The helical ABF can "swim" under weak magnetic fields. Both propulsion and steering motion can be achieved [11, 13, 14]. With appropriate functionalization, the ABF was able to complete the mission of drug delivery [13, 14, 18], and the drug release can even be thermally triggered [14]. Xu et al. [63]reported magnetic field-guided nanospears for targeted and high-throughput intracellular gene delivery, in which the sharp tips of the

nanospears allow for physical penetration of the nanospears through the cell membranes.

Powering micromotors by acoustic waves was also a promising approach due to the simplicity. Since the acoustic wave is isotropic, it is usually combined with magnetic field for direction steering. For example, Mallouk and coworkers [15] developed magnetic Ru–Ni–Au nanowire motors, which were moved by acoustic field and steered by magnetic field. These nanowires were excited by ultrasonic standing waves with resonance frequency of 3.77 ± 0.01 MHz. The magnetic filed can ensure the unidirectional motions of the nanowires.

In addition, the electrical field was also explored to power and steer micromotors at subcellular level. It is also called "electric tweezers," which was contributed by Fan and her coworkers [16, 64]. "Electric tweezers" have been broadly used to control the mechanical motions of a variety of nanoscale entities made of a range of different materials from metals, semiconductors and even insulators. Electric tweezers have great advantages in the manipulation precision when compared to other manipulation techniques. Both moving speed and moving direction can be independently controlled by the AC and DC electric fields. A precision of sub-200 nm, and high-speed rotation motion > 18,000 rpm and controlled assembling into arrays can be easily achieved by using electric tweezers. Recently, Liang et al. [65] reported visible-light-gated reconfigurable rotary actuation of electric nanomotors with added degree of control. Besides, electric tweezers also have been utilized to manipulate multifunctional micromotors for single-cell biosensing, real-time monitoring, drug delivery and controlled drug release, which is a successful demonstration of prototype biomedical nanorobots [66–74].

Biomedical applications

Micromotors have perfect dimensions that match the building blocks of life, i.e., the cells. These micromotors can move freely either in vivo or in vitro, toward realizing complicated missions, such as cargo (e.g., drug, DNA, cell) delivery, biosensing, cell isolation, surgery and many more. In the following, we highlight some representative works on these applications.

Cargo delivery

Micromotors present unprecedented opportunities to revolutionize the targeted drug delivery. The powering energy provided by micromotors could greatly enhance the chance to penetrate into cells or tissues such as tumors. This section will discuss the exemplary cases that delivered therapeutic drugs that acted upon the targeted cells extracellularly or intracellularly. Some representative applications are summarized in Tables 1 and 2, and shown in Fig. 2.

The early-stage (Table 1) micromotors were made of simple geometry, such as wires [4–7, 19]. The nanowire motor was tested capable of picking up, transport and release particles carrying therapeutic molecules [4]. But clearly there was huge space to improve. More innovations and higher degree of complicacy of the structures enabled more effective drug delivery. Not only the mobility of the micromotors can be improved, which increased the chance of successful delivery, but the precise motion control can be achieved and the smart responsive switch can also be integrated to the micro/nano vehicle. For example, Bradley J. Nelson and his group developed artificial bacteria flagella whose bio-mimicking helical structure achieved fuel-free delivery of hydrophilic model drug to myoblast cell [13]. The same laboratory later functionalized it with the temperature-sensitive dipalmitoylphosphatidylcholine (DPPC)-based liposome, realizing the temperature-dependent release of celcein at 39–41 °C [14]. Qiang He's group [26] developed a layer-by-layer assembled nanorocket that contained both the Pt catalyst and magnetic Fe_3O_4 nanoparticles. The catalysis provided energy, and the magnetic Fe_3O_4 was used to orientate the nanorocket under magnetic field. With both powering and orientating capability, the nanorocket delivered doxorubicin (DOX) to the vicinity of HeLa cells. Qiang He's group also developed sub-100 nm scale Janus nanoparticles (< 75 nm) [35]. The sub-100 nm silica nanoparticles conferred mesopores, such that the cargos can be loaded into the pores. The propelling energy from the micromotors significantly enhanced the ability of the nanoparticles to enter HeLa cells, as the speed can go up to ~ 20 μm/s. DOX was loaded to the pores and slowly released intracellularly (Fig. 2a [35]). Also, Sanchez's group [42] extended the Janus silica mesoporous nanoparticles to different sizes under 100 nm and loaded and released Rhodamine B (RhB). The same laboratory further developed Janus silica mesoporous nanoparticles that were powered by the decomposition of urea at physiological concentration [75]. The decomposition can be activated by urease and will produce NH_3 and CO_2. Interestingly, the decomposition reaction can be turned off by Ag^+ or Hg^+ and turned on by dithiothreitol (DTT), which enabled a reversible control. The directional movement is directed by magnetic field after incorporated with Fe.

A grander challenge for micromotors system is the in vivo drug delivery. Recently, pH-dependent micromotors were designed and tested in mice [47, 76]. The Zn-based micromotor starts propulsion at acidic environment, and thus it is promising for drug delivery to stomach tissue [76]. For the delivery to intestine, they modified the design (Fig. 2e) [47]. The magnesium-based water-driven micromotors covered with enteric polymer coatings were prepared and tested [47]. The enteric polymer coatings were stable in the acidic envi-

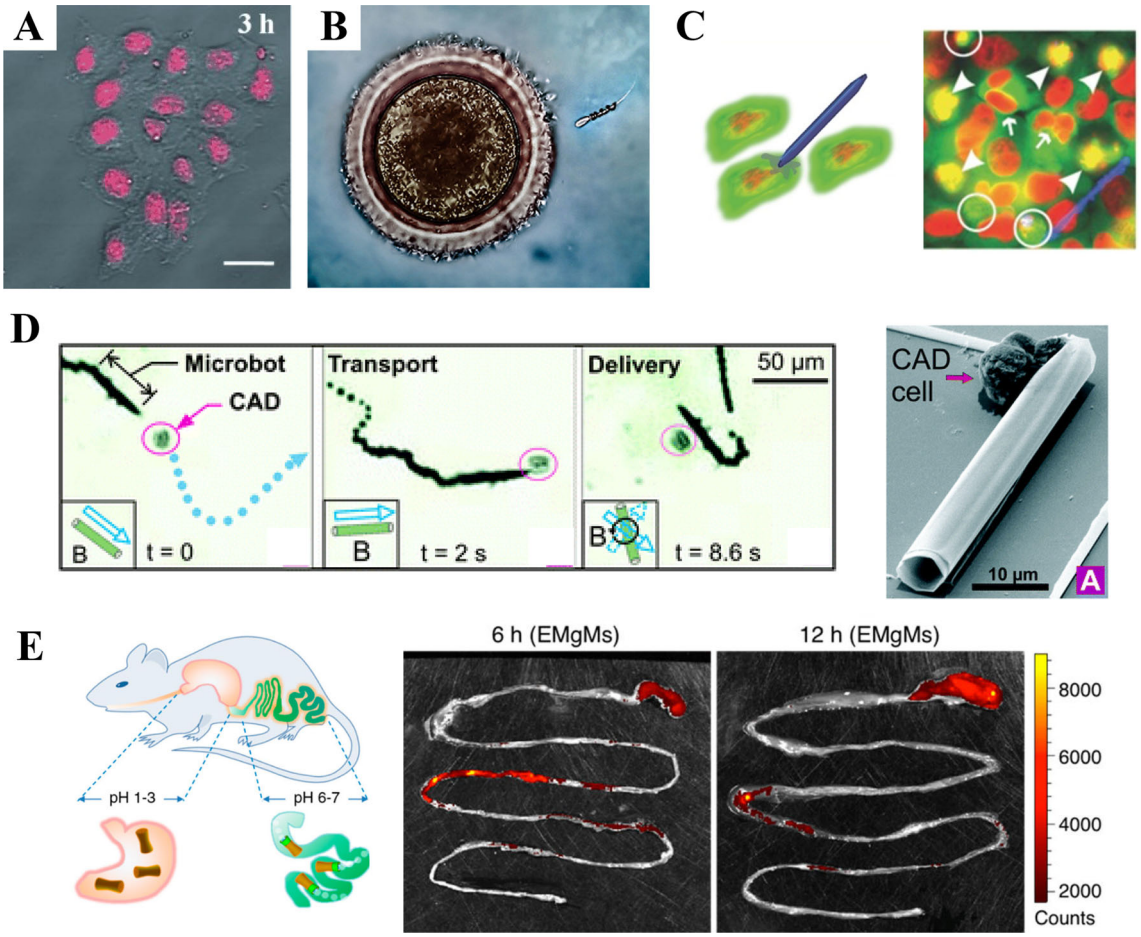

Fig. 2 Example biomedical applications of micromotors. **a** Fluorescence image overlaid with DIC channels of HeLa cells and DOX (red) released from Janus mesoporous silica nanoparticles. Scale bar 10 μm. Adapted and reprinted from Ref. [35]. **b** A helical micromotor capturing and transporting an immotile but functional sperm toward an oocyte under rotating magnetic field. Adapted and reprinted from Ref. [81]. **c** Dual-action microneedles conducting the drilling of HeLa cells and delivery of camptothecin. Adapted and reprinted from Ref. [84]. **d** A Ti–Fe–Pt microtube captures, transports and releases the neuronal cell. Reprinted from Ref. [17]. **e** In vivo micromotor enhanced drug delivery in the GI tract of mice. The propulsions of the Mg micromotors were turned on once the pH-sensitive PEDOT coatings were degraded. Right figures: Superimposed fluorescence images showing the in vivo distribution of motors in the GI tract of mice at 6 h and 12 h post-administration. Red color shows the micromotors loaded with red fluorescent dye. Reprinted from Ref. [47]

ronment of stomach but dissolved in the neutral-to-alkaline environment of intestinal fluid. As a result, the micromotor was exposed and the propulsion took place spontaneously after the micromotor entered the intestine. The study showed enhanced retention of micromotor in the GI tract of mice [47]. These two pioneering proof-of-concept studies claimed the transition of micromotors from in vitro to in vivo stage.

Biosensing

A micromotor-based bioassay was reported to detect nuclei acid. [77] The thiolated capture probes will capture the complementary nucleic acid target, which will then capture an Ag-tagged probe. After stripping off from the thiolated capture probes and placing in H_2O_2, the nanowire will be powered by Ag^+ catalyst. The motion speed will be proportional to the quantity of the Ag^+ that can accurately reflect the quantity of the nucleic acids. The method can also be applied to other biomolecules. The same laboratory [6] also pioneered ultrasonically powered Au–Ni–Au nanowire motors that selectively captured bacteria and biomolecules. They functionalized the surface of Au sections with receptors for specific target to perform "on-the-fly" capture and transportation of *E. coli* and Concanavalin A. On a step forward, Joseph Wang's laboratory utilized the "on-the-fly" capturing function of micromotor to establish a lab-on-a-chip immunoassay which could compete with ELISA due to the no need of washing step [78]. The anti-immunoglobulin (IgG) receptor was conjugated to PEDOT-COOH coating on a micromotor. The anti-IgG-modified micromotor will

perform "on-the-fly" capture to the IgG antigen. This work illustrated that the antibody-modified micromotors can be used for recognition and transportation of proteins with high selectivity.

Cell manipulation

In addition to delivering drugs or biomolecules, the micromotor can also transport cells as long as the driving force is sufficient and the catching and releasing are easy to perform. Samuel Sanchez et al. [17] developed a Ti/Fe/Pt micron tube that carried out the mission of loading, transporting and releasing single neuronal cell despite the relatively large size and weight of the cell cargo (Fig. 2d). Interestingly, the releasing was achieved by rapidly turning the magnetic field. Recently, David H. Gracias's group [79, 80] developed a microgripper, which performed the thermally or chemically triggered capture and release of single object or cell. These tetherless microgrippers can perform a series of "gripping" action like human hand, as shown in Fig. 1h [80]. They are the promising tools for precise cell manipulation.

A clinically relevant application of cell manipulation is that on sperm cell. Micromotors are a promising tool for assisted fertilization. The current study was able to assist immotile, but functional sperm to move to oocyte, thus enhancing the chance of fertilization, as shown in Fig. 2b [81].

Micro-/nanosurgery

Micromotors are the foundation of miniature tools for minimally invasive surgery. Solovev et al. [82] utilized a nanotube to pick and transport a yeast cell. Xi et al. [83] further explored the idea of the roll-up tubular nanotube motors as potential tools for nanosurgery. The sharp-tipped micromotors performed drilling into soft tissues ex vivo under the control of magnetic field. The microtools demonstrated the potential for minimally invasive surgery. In another study [84], microneedles were used to perform surgery on single cell, delivering drugs to kill local HeLa cells (Fig. 2c). Studies also focused on the capability of the micromotors to penetrate tissue barrier. Joseph Wang and coworkers reported ultrasonically powered high-speed microbullets [85]. The perfluorocarbon emulsions were vaporized by the ultrasonic field to generate an average thrust speed of 6.3 m/s, a record high by the time of publication. Recently, a wound-welding dye consisting of magnetic Janus silica nanoparticles was developed [86]. The magnetic Janus silica nanoparticles can travel against the bleeding flow due to the mobility powered by magnetic field and the thermophoretic effects. The utilization of magnetic Janus nanoparticles improved the depth of welding in strong bleeding. It could replace the currently used wound suture used in surgery.

Summary and prospects

This review summarized important aspects of micromotors. The difference between the macroscopic and microscopic motion was discussed. The progresses of micromotors were closely associated with the advents and optimization of novel fabrication techniques, which was highlighted. The different powering and navigation strategies were compared. The examples of the biomedical applications were introduced. The past progress and present challenges of micromotors were also discussed. As a whole, this article provided comprehensive review to the domain of micro/nanomotors and stressed on the relation between the device designs, manufacturing techniques and the biomedical applications. We also underlined fundamental knowledge and innovative strategies that could inspire prospective convergence of interdisciplinary knowledge to push forward the micromotors toward biomedical and clinical applications.

Predictably, the future studies of micromotors will focus on achieving better motion control, propulsion velocity and functionality. Further scaling down, the nanoscale motors must overcome the random thermal collision from the fluid molecules. Ultrahigh propulsion velocity could be one promising solution. Environment-responsive functions should be paid great attention to for it ensures the motors to travel to different regions in the body and to perform their tasks at specific position. Meanwhile, novel types of chemical fuels and the employment of biodegradable materials could minimize the health concern associated with the micromotors, thus reducing the regulatory challenges. It can be expected that the micromotors at current stage are an attractive solution to various in vitro tasks, such as gene delivery for gene-editing systems, assisted fertilization and biomolecule detections. However, more efforts must be made to fully exploit their potential in the in vivo applications. Lastly, any materials interacting with living organism must be always treated with stringent examination of its toxicity, locally and systemically. The safety of nanomaterials is still under fierce debate. The evaluations of micromotors in vitro and in vivo are currently scarce in the literature. It must be fully understood before the clinical translation of micro/nanoscale motors and devices.

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