Recent Advances in Motion Control of Micro/Nanomotors

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Micro/nanomotors are able to convert energy in different forms into propulsion and movement with predesigned directions and velocities, enabling them to be self-propelled carriers and vehicles for the delivery of active pharmaceutical ingredients and other biomedical cargos to the target sites such as tumors. However, the inadequate energy and noncontrollable moving directions remain the grand challenges for their promising applications. Recently, an increasing attention has been paid to these issues and numerous reported researches have focused to design and develop more efficient and precisely controllable micro/nanomotors with different methods. This review aims to summarize those studies and to introduce newly developed micro/nanomotors including synthetic micro/nanomotors and biohybrid motors, discussing the control mechanisms as well as advantages and limitations thereof. Conclusions and future perspectives are also provided in brief.

1. Introduction

In the past decade, micro- and nanoscale devices have stimulated considerable attention due to their promising applications in sensing, tracking, decontamination, and biomedical areas. In particular, micro/nanomotors with desirable dimensions, promising potential of active targeting abilities as well as autonomous or semi-autonomous mobility in a predesigned direction with tuned velocity have paved the way for designing multifunctional drug delivery systems.

Initially, a wide range of technological developments started from the synthetic micro/nanomotors and various types of such micro/nanomotors have been successfully fabricated, such as microtubes, nanowires, Janus micro/nanomotors, and helical micro/nanomotors. In addition to the diversity of shapes, increasing researches have been devoted to the propulsion and motion control. In general, these micro/nanomotors are propelled either by self-produced energy such as bubble propulsion, self-electrophoresis, or surface-tension gradient mechanisms, or with the aid of an external energy including light, magnetic or electrical fields, or acoustic waves. Those would be discussed with details in the following sections.

Despite the enormous amount of research effort being made on those synthetic micro/nanomotors as well as their impressive capacities including remarkable speeds and large cargo-towing forces, the insufficient biocompatibility, the toxicity of the chemical fuel used in the chemotactically controlled micro/nanomotors, and the special manipulating equipment required for the external guidance tremendously hinder their potential applications.

To reduce and eliminate those limitations, new efforts have been made to design and develop biohybrid micro/nanomotors consisting of both artificial and biological parts by mimicking the specific traits of living organisms. Those novel biohybrid micro/nanomotors offer impressive capacities including superior biocompatibility, possible autonomous motion control when being placed in biofluids due to specific chemotaxis, and high efficiency in achieving predesigned functionalities.

The difficulties in applying those artificial and biohybrid micro/nanomotors in pharmaceutical and biomedical industries lie in their nondurable propulsion and uncontrolled mobility, which not only makes the motor systems unstable but also extremely challenges their designed functionalities. Recently, increasing attention has been paid to unlock this critical bottleneck and various approaches to achieve motion and direction control of these motors have been reported, either by applying self-propelled motions or utilizing external fields such as light, magnetic, acoustic, or electric field control. The present review aims to summarize those most recently published studies and make in-depth discussion on the advantages and disadvantages of each approach, as well as
their potential applications in pharmaceutical and biomedical industry.

2. Synthetic Micro/Nanomotors

Artificial machines in microscale that mimic the behavior of biomachines in the biological systems is promising in precisely performing complicated tasks. However, it is difficult to control those machines especially in micro/nanoscale due to low Reynolds number and significant Brownian motion for small objects.\(^{[28,29]}\) In general, the motion of those artificial micro/nanomotors are produced either by self-propelled method or by adding an external energy. One of the most common approaches to guide the locomotion of the self-propelled micro/nanomotors is the chemotactic control, in which chemo-attractants and chemorepellents are utilized to produce a chemotactic behavior in a directed motion toward and away from a concentration gradient, respectively. In addition, specific shapes as well as surface morphologies and properties have been proved useful for further promoting the chemotactic control. Other special form of chemotaxis includes pH-taxis, and temperature-taxis also have attracted increased attention due to ease of application.

For the micro/nanomotors driven by an external field, improved motion control both spatially and temporally could be accomplished thanks to the external forces induced by the applied field. In addition, the speed and direction of the motion can be precisely manipulated by adjusting the intensity and the direction of the field. Also, an intriguing on/off motion can be achieved by properly switching the applied external field.

2.1. Self-Propelled Micro/Nanomotors

Self-propelled micro/nanomotors have attracted abundant interest not only due to their simple shapes and unsophisticated fabricating techniques but also because of being a primary model for studying complex behaviors of more complicated micro/nanomotors yet with promising implementations in various fields. Understanding the motion-control mechanisms (see Table 1) and their locomotion traits of these self-propelled micro/nanomotors could pave a basic way to further improve the designed multifunctional systems based on those micro/nanomotors.

2.1.1. Bubble Propulsion

Bubble-propelled micro/nanomotors are designed based on a simple concept where the propulsion is provided by the numerous bubbles produced either through chemical reactions, such as the degradation of a chemical reagent (e.g., hydrogen peroxide, \(\text{H}_2\text{O}_2\)) with a catalyst under specific conditions, or some redox reactions producing gases spontaneously. The propulsion results from the recoil effect\(^{[30]}\) caused by the detachment of numerous bubbles gathered at the tail of the micromotor, as shown in Figure 1. As the bubbles reach the detachment radius and start to detach themselves, the detachment results in a momentum change which induces a driving force (F) away from the tail surface. Initial detachment velocity of bubbles in horizontal is not zero, so there are two kinds of velocities present which is \(V_x\), the horizontal velocity, and \(V_y\), the vertical velocity. In this instance, \(V_x\) is the predominant velocity, thus it produces a higher momentum which makes the whole body move forward, away from the catalyst part.

Based on this principle, some micro/nanomotors with different shapes and solution media or with alternative catalyst would allow the bubble-propelled micro/nanomotors to exhibit different characteristics in terms of motion. Shapes such as microtubes, microwires, and Janus are desired for this type of propulsion. It is interesting to note that the geometry of the bubble-propelled micro/nanomotors has been increasingly utilized to foster a more controllable motility of these motors, and novel fabrication methods that are capable to produce versatile micro/nanomachines with diverse geometries have also been reported. Su and his co-workers\(^{[31]}\) developed a novel bubble-propelled micromotor with a well-engineered hierarchical porous structure (Figure 2A), which could be fabricated in one-step from microfluidics with controllably and spontaneously evolved double emulsions. The hierarchical porous structure of the micromotor consist two well-aligned microscale pores, which...
was incorporated in nanoporous matrix. The motility of the micromotors was produced and controlled by the decomposition of H2O2 by the Fe3O4@Ag nanoparticles decorated in the opening hole of one microscale pore at the bottom of micromotor. These micromotors with special structures are capable to capture the oil pollutants in water and could be easily recovered by applying an external magnetic field. Also, the microfluidic emulsions-based approach is promising to continuously and controllably fabricate these novel micromotors with sophisticated structures and versatile functions.

By taking advantage of such motion-controlling approach, Zhang et al.\textsuperscript{[32]} presented a chemically powered jellyfish-like micromotor (Figure 2B). To mimic the umbrella-shaped body and the muscle fibers on the inner umbrella of the jellyfish, the designed micromotor was structured with a multilamellar shell and a DNA assembly with catalase decorations modified on the concave surface. The motion control of this micromotor was achieved by the catalytically generated oxygen gas by catalase on the concave surface. The motion control of this micromotor was structurally a multimetallic shell and a DNA assembly with catalase decorations modified on the concave surface. The micromotor was controlled from nearly spherical, hemispherical to crescent-shaped by adjusting the volume ratio of the two immiscible oils (ethoxylated trimethylolpropane triacylate/paraffin oil) in the initial emulsion. The size of the obtained micromotor was controlled by varying the fluid flow parameters. Flexible functionalities of the micromotors could be achieved by incorporating functional nanoparticles into the asymmetric structure. The motion of the specific micromotor in the reported study was controlled by the bubble propulsion produced by the catalyzed H2O2, whereas the direction of the micromotor was manipulated by the Fe3O4 nanoparticles.

Although sufficient propulsion has been ensured by those bubble-propelled micro/nanomotors with H2O2 as fuel, efforts are still needed to design and develop new micro/nano machines with biomaterials exhibiting adequate biocompatibility and biodegradation ability. These new micro/nanodevices with low toxicity and favorable biocompatibility show preferable motion capabilities in biofluids. Zhou et al. developed a multilayer micro/nanomotor consisting of a Zn core, a thin Fe intermediate

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### Table 1. Self-propelled micro/nanomotors.

| Propulsion mechanism     | Motor type                                | Propulsion source and motion control                                      | Potential applications                                      | Ref. |
|--------------------------|-------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------|------|
| Bubble                   | Hierarchical porous structure micromotors | Bubble with H2O2 as fuel and asymmetric geometries                          | Water decontamination                                       | [31] |
| Jellyfish-like micromotors | Bubble with H2O2 as fuel and asymmetric structure | DNA sensing and detection                                                  |                                                             | [32] |
| Fe3O4-nanoparticle-containing mesoporous SiO2 microparticles | Bubbles with H2O2 as fuel and asymmetric structure | Water remediation and cargo transport                                        |                                                             | [33] |
| Janus micromotors with nanoparticles of Fe3O4 and MnO2 | Bubbles with H2O2 as fuel and asymmetric structure | Wastewater treatment                                                        |                                                             | [34] |
| Self-electrophoresis     | Au/Pt micromotor                          | Self-electrophoresis and asymmetric geometries                            | Biocompatible engine                                        | [40] |
| Bimetallic nanomotors    | Self-electrophoresis and asymmetric geometries | Microscale cargo transport                                                  |                                                             | [41] |
| Platinum micromotor with a shape of twisted star | Self-electrophoresis and geometries and shapes | Diverse biomedical applications                                              |                                                             | [3]  |
| Surface-tension gradient | Solid agglomerate particles               | Self-generated gradient and chemotactic control                           | Offer insight into the propagation                          | [44] |
|                          |                                           |                                                                           | of pollutants                                               |      |
| Droplet swimmer          | Predesigned gradient and chemotactic control |                                                                            | Dynamic sensing                                              | [45] |

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**Figure 1.** Force and velocity schematic of bubble-propelled micro/nanomotor in the media.
layer, and coated with (poly (aspartic acid), PASP) on the surface; all of these materials are biodegradable. They used gastric acid as a solution media and the micro/nanomotor exhibited ability to carry drug and locate in target site, which show huge potential in biomedical application.\[35\]

Bubble-propelled micro/nanomotors with powerful driving force and desirable biocompatibility are very advantageous and promising in biomedical applications as long as they are further improved with precise motion control and prolonged durability of the propulsion.

2.1.2. Self-Electrophoresis Propulsion

Self-electrophoresis refers to the self-propelling ability of microorganism, which occurred in biological systems through aqueous media by ion exchanges with the surrounding solutions, which was first proposed by Peter Mitchell, a Nobel laureate.\[36\] Mimicking this feature, self-electrophoresis-propelled micro/nanomotors have been designed and fabricated. The motion of these micro/nanomotors were propelled by harvesting chemical-free energy from surrounding environments and transducing it to mechanical energy via self-electrophoresis.\[37\] A theoretical analysis for the mechanism of the self-electrophoresis-propelled micro/nanomotors has been reported by a previous study.\[38\] As shown in Figure 3A, a conducting microparticle produces an electric field as a result of redox chemistry occurring at its two ends. At the anode end of the particle, oxidation of B sets up an electron flow to the cathode end, where those electrons are consumed by the reduction reaction of A. At the same time, protons are also generated at one end (anode) and consumed at the other end (cathode). The migration of those protons drags the surrounding fluid with them, pushing the microparticle in the opposite direction.\[39\]

Compared with the bubble-propelled micro/nanomotors, self-electrophoresis-propelled ones show certain axiality, such as toward one end of the motor. Accordingly, Moran and Posner designed and fabricated an Au/Pt micromotor,\[40\] where
the platinum end serves as the anode and the gold end as the cathode. Fluid flow would be formed and transferred from the platinum to the gold end under the autogenic electric field and propelled the negatively charged micromotor with the platinum end forward. In addition, self-electrophoresis-propelled micro/nanomotors could also produce a rotatory movement, which has attracted considerable attention in recent years. Wang et al. developed bimetallic Au/Pt nanomotors; they validated that the interactions between the two nanomotors would attract each other and form a staggered doublet that begins to rotate immediately.\(^{41}\)

It is also interesting to note that the motions of micro/nanomotors could be rationally guided by controlling the shapes of such microparticles. Brooks et al.\(^{[5]}\) designed and fabricated micromotors based on solid platinum using projection lithography to form thin plates shaped as twisted stars with n-fold rotational symmetry (Figure 3B), which could rotate steadily with speed and direction specified by the type and extent of shape asymmetry. With further necessary experimental studies, such rotary motions of active matter comprised of self-rotating units could provide promising biomedical applications such as colloidal machines.

Although self-electrophoresis-propelled micro/nanomotors are more advantageous than the bubble-propelled ones in terms of motion control, there are still some issues that need to be considered for the future research. First, most of the self-electrophoresis-propelled micro/nanomotors are short of sufficient motion energy, leading to an inadequate durability. Also, most of the applied solution media such as H\(_2\)O or hydrazine are toxic, which hinders their applications in pharmaceutical and biomedical areas. Furthermore, the motion of these self-electrophoresis micro/nanomotors is easily disturbed under circumstances with high ionic strength, adding obstacles to its potential applications in biological fluids.

2.1.3. Surface-Tension Gradient Propulsion

Surface-tension gradient is formed between two different types of liquids due to the differences in their interfacial energy caused by the inhomogeneity of solute concentration. The interfacial energy gradient could easily cause a mass flow and such mass flow can efficiently propel those micro/nano sized objects, which is referred as the Marangoni effect.\(^{42}\) These micro/nanomotors propelled by the surface-tension gradient are promising to exhibit chemotactic behavior,\(^{2}\) which is capable to achieve the predesigned motility with a desirable directivity in the liquid surrounding.

Predesign of the surface tension gradient is requisite before fabricating such a micro/nanomotor propelled by the Marangoni effect. Basically, there are two approaches that could produce the surface-tension gradient. One is a self-generated method to produce the surface-tension gradient by accomplishing an asymmetric release of a preformulated chemical from the micro/nanomotor.\(^{43}\) Pumera and co-workers took the lead in fabricating a solid hydrophobic agglomerate which could move itself in deionized (DI) water through the Marangoni effect generated by the surface-tension gradient changes. The changes were caused by the asymmetric spontaneous dissolution process of the agglomerate.\(^{44}\) They also compared the motility traits of this solid agglomerate in several liquid media, such as sea water and water with 5\% of surfactant. It was observed that the agglomerate commonly showed the random movement in the different liquid media and only exhibited a subtle velocity difference.

The other is a predesigned approach to create the surface-tension gradient directly by composing the formulation of the solution media. Comparing with the self-generated method with inadequate controllability, this predesigned approach is a preferable alternative method due to its exceptional capability of boosting a more controllable motility. Francis et al. designed a special floating droplet swimmer composed of an ionic liquid of tris-(hexyl)(tetradecyl)phosphonium chloride, which is able to detect a concentration gradient of the anions and cations.\(^{45}\) The surface-tension gradient could be fostered artificially and controllably by increasing the concentration of the Cl\(^{-}\) in solution, resulting in a modulation of the aqueous solubility of the cation; thus, a movement with a desirable direction of the droplet swimmer is generated.

Unfortunately, most of these motor objects reported by previous studies are relatively far from being “nano” or even “micro.” Hence, lately efforts have been made not only to further improve the motility of such motors but also to minimize these fabricated motors within a satisfactory scale. Peng and co-workers\(^{46}\) fabricated a bowl-shaped poly(ethylene glycol)-b-polystyrene nanomotors with an average size of 308 nm entrapped with platinum nanoparticles in the cavity, while a model drug was encapsulated in the inner compartment. Directional movement of the nanomotors in the presence of a gradient of hydrogen peroxide produced by hydrogen peroxide–secreting neutrophil cells, was observed in both static and dynamic systems using glass channels and a microfluidic flow. This nanomotor is capable to act as drug delivery vehicle that are able to actively seek and precisely locate targeted tissues using concentration gradients of signaling molecules.

Despite the promising application potentials of such motors propelled by the surface-tension gradient, most of the reported studies barely involved such motors in a desirable micro/nano scale. In addition, the acceptable motility performance could only be accomplished in an unsophisticated liquid media. Consequently, further researches are necessary to obtain a more controllable motility of motors, particularly in micro/nano size, propelled by this principle.

No matter which propulsion source the micro/nanomotors relied on, it should be noted that the morphologies and topographical features\(^{47}\) of such self-propelled motors, including shapes and surface properties\(^{49}\) such as wettability and roughness,\(^{50}\) could play a crucial role in their motion control. Sánchez and co-workers\(^{51}\) reported a methodology to break the time-reversal symmetry of particle trajectories so as to direct the macroscopic flow of the micromotors by exploiting a phoretic and hydrodynamic interactions of synthetic micromotors, particularly with local topographical features. It is interesting to note that both the orientational alignment induced by the topographical features and the geometrical asymmetry of the micromotors played a critical role in producing a directional particle flow.

Apart from the shape and topographical features, surface wettability could also be utilized to direct the motion of the chemically driven motors. One typical example is the nanoflask motors presented by He and co-workers,\(^{52}\) which could swim autonomously in the solution of glucose directed by their surface wettability alone. The motors were propelled by the enzymatic
cascade reaction of glucose oxidase and catalase inside the nanoflask. They claimed that the transition between a puller-like flow field generated by the hydrophilic nanoflask motor and a pusher-like flow field created by the hydrophobic motor could be accomplished only by adjusting the surface wettability of the motors. This work is capable to offer a fundamentally different strategy to manipulate the direction of movement of micro/nanomotors.

Despite those talented idea of utilizing morphologies and topographical features to nicely direct the locomotion both in velocity and direction, those attempts are still in their early stage. Before that, an even bigger problem is how to produce those shapes in a controllable and precise way. Wilson and co-workers have reported a general methodology capable to accurately control the shapes of polymersomes via the addition of polyethylene glycol (PEG) under nonequilibrium conditions at the nanometer scale. By adjusting the water content and the PEG concentration, various shapes were uniformly captured. They also proposed a method to produce reshaping polymersomes using Hofmeister effect, which has been confirmed as an efficient tool to tailor the shape of polymersomes into various morphologies.

2.2. External-Field-Propelled Micro/Nanomotors

Although the self-propelled micro/nanomotors have shown excellent performances in fostering the requisite energy, and promising potentials in controlling the motility with desirable direction, most of the reported micro/nanomotors still utilized one or more external energy sources, such as light, electric field, acoustic wave, or magnetic field, to accomplish a boosted propulsion with a more controllable motility (see Table 2). Details of these external-field-propelled micro/nanomotors would be discussed in the following subsections.

2.2.1. Light

Light is a common renewable energy source, which could be easily propagated remotely. The idea of light-propelled micro/nanomotors originated from the light-coupled transport process, which was first envisaged by Jean-Marie Lehn in the 1980s. In recent years, as an efficient external energy for driving the micro/nanomotors, light source has been explored in-depth to fulfill an acceptable and satisfactory motility controllability. Basically, the movement of the light-propelled micro/nanomotors is activated either by photochemical reaction, photothermal effect or photochromism; both could avoid the utilization of toxic chemical fuels. However, the absence of those chemical fuels leads to a very challenging issue of achieving high velocities for these light-driven micromotors. Fortunately, various combinations of materials with excellent catalytic performances could be applied in the motor systems to obtain sufficient or even controllable moving velocities.

One of the intriguing advantages of light-driven micro/nanomotors is that a manipulator could be utilized to start and stop the light source easily and freely, ushering in a

| External-field | Motor type | Propulsion source and motion control | Potential applications | Ref. |
|---------------|------------|-------------------------------------|------------------------|-----|
| Light         | Isotropic semiconductor micromotors | UV light irradiation and asymmetric photocatalytic reactions | Micro/nanoengineering such as manipulating nanocargoes | [69] |
| Light         | Tadpole-shaped Si–Au microswimmers | Visible light-induced self-electrophoretic propulsion and shape | Analytical, biomedical, and environmental applications | [71] |
| Light         | Single-component BiVO₄ micromotors | Visible-light irradiation and asymmetric morphology | Sensing, bioreactors, and cargo delivery | [17] |
| Light         | Half-metal-coated Janus microparticles | X-ray radiation and different radiation dose | Medical imaging or nondestructive testing | [72] |
| Electrical field | Au–SiO₂ Janus micromotor | Induced-charge electrophoresis and asymmetric structure | Diverse biomedical applications | [79] |
| Hybrid colloidal microswimmers | Electric field and geometries | Cargo pick-up and transportation | [80] |
| Spherical colloids with metal patches | Electric field and field strength and patch geometry | Cargo transportation | [81] |
| Metallodielectric Janus particles | Electric field and asymmetric electrical polarization of particles | Collection of microparticles | [82] |
| Magnetic field | Microtubes | Magnetic energy and geometries | Encapsulation, delivery of cells and other cargoes | [90] |
| 2D microswimmer | Magnetic energy and geometries or chirality | Diverse biomedical applications | [91] |
| Walnut-like micromotor | H₂O₂ fuel and external magnetic field | Environmental remediation | [92] |
| Hydrogels-based Janus micromotors | Magnetic energy and temperature | Biomedical and water purification | [15] |
| Acoustic field | Metallic microrods | Acoustic energy and geometries | Versatile micromachines | [101] |
| Nanowires and hollow tubes | Acoustic energy and topographical manipulation | Rotatory microengines | [102] |
| Gold microplates with twisted star shape | Ultrasound energy and geometries | Sample isolation, drug transportation, etc. | [103] |
| Gold nanowire with polymer coating | Ultrasound energy and geometries | Intracellular drug delivery | [104] |
switchable moving mode of micro/nanomotors in the presence or absence of light. In addition, such micro/nanomotors can be programed to move in a controllable manner along the designed trajectory by adjusting the direction of light irradiation. Chen et al.[69] designed and fabricated intelligent photoresponsive microparticles of isotropic TiO$_2$ (Figure 4A), taking advantage of the limited penetration depth of light to establish asymmetric photocatalytic reactions over them and produce a directional net O$_2$ concentration gradient independent of Brownian motion.[70] The results of this study showed that the start and stop of the motion are controlled through the applying and withdraw of light source, whereas the micromotor can move along the predesigned path control achieved by changing the direction of incident light.

Apart from reversibly controlling the onset as well as designing directional trajectory of the micro/nanomotors, light intensity could also be regulated to establish a controllable velocity of such motors. Zhou et al.[71] developed and prepared a light-driven Si–Au micromotor using glancing angle deposition technique. With a shape of tadpole (Figure 4B), these micromotors could be activated by visible light, leading to a movement with a modulated velocity in certain solutions including DI and organic solvents. Villa et al.[17] presented BiVO$_4$ micromotors with single-component with well-defined micro/nanostructures (Figure 4C). Under visible-light irradiation, these micromachines could swim both individually and as collectively assembled entities, and they also showed interesting selectivity of seeking and adhering to the yeast cell walls, with the possibility to manipulate their attachment/release by switching the light on/off, respectively. As a result, using an external light source, these sophisticated micro/nanomotors are capable to fulfill diverse tasks including sensing, biohybrids assembly, and cargo delivery in complex environments.

Light with different wavelengths from UV to NIR exhibit distinct properties, most of which have been successfully used to propel light-responsive micro/nanomotors.[19] However, the low penetrability of UV and NIR as well as visual light hinders their applications. X-ray, as a popular light source with adequate penetrating power, has been widely applied in various fields such as medicine and biology. Lately, Xu et al.[72] first fabricated half-metal-coated Janus microparticles propelled by X-rays in aqueous solution (Figure 4D). The observed motion propelled by X-rays followed the bubble growth fostered by the water radiolysis near the particle surface under X-ray irradiation. This work revealed that the propulsion speed of the half-metal-coated Janus microparticles could be remotely controlled by varying the radiation dose of X-rays. This is a noteworthy finding due to its promising potentials in using light-powered micro/nanomotors in opaque environments.

Despite the success of designing and fabrication of the light-propelled micro/nanomotors, there are still limitations that make it challenging to practically apply those motors in pharmaceutical and biomedical areas. In an effort to overcome those challenges, the following aspects need to be considered for future researches. First, light-propelled micro/nanomotors needs to be better designed and further improved to accomplish a precise motion.

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**Figure 4.** Representative examples of light-driven micro/nanomotors. A) Schematic diagram of the 3D tubular micromotors with single exposure of femtosecond optical vortex. Reproduced with permission.[69] Copyright 2017, Wiley-VCH. B) Schematic diagram of the propulsion mechanism of the Si–Au micromotors activated by visible light in DI water. Reproduced with permission.[71] Copyright 2017, Royal Society of Chemistry. C) Schematic diagram of the visible-light-driven single-component BiVO$_4$ micromotors with the autonomous ability for capturing microorganisms. Reproduced with permission.[17] Copyright 2019, American Chemical Society. D) Schematic diagram of the X-ray-powered micromotors. Reproduced with permission.[72] Copyright 2019, American Chemical Society.
manipulation with designed direction and desirable velocity and durability in a more complicated environment, enabling it with promising applications in complex biofluids. In addition, it is necessary to exploit new light source with acceptable and satisfactory penetrating ability as well as excellent biocompatibility, as substitute of X-rays. Finding alternative fuels with low toxicity and high efficiency is also indispensable to further ameliorate those micro/nanomotors.

2.2.2. Electric Field

Micro/nanomotors could also be propelled by utilizing an external electric field.[73-75] Although there are many distinct advantages exhibited by the direct current (DC) electric field,[76] the alternating current (AC) electric field is more commonly applied so as to eliminate the electrophoresis. In AC electric fields, asymmetric micro/nano devices and diode motors are propelled by the potential energy produced through induced-charge electrophoresis (ICEP) and self-rectified electroosmosis respectively, which would be discussed in detail in the following sections.[77]

The ICEP is the most commonly applied approach driving the asymmetric micro/nanomotors with different shapes or polarizabilities in the AC field. The asymmetric micro/nanomotors are polarized by the AC field; this induced an asymmetric accumulating counter charge in the electric double layer (EDL) around the motors, generating an electro-osmotic flow of these motors driven by the AC field with a direction dictated by the type of the motors as well as the direction of the field. The asymmetric EDL could be produced by the different polarizabilities of the constituent materials of the motors. The more polarizable half of the EDL would accumulate more charges, forming stronger induced-charge electro-osmosis (ICEO) to propel the asymmetric micro/nanomotors with a direction of the less polarizable side facing forward.[78] Dou et al. fabricated an Au–SiO₂ Janus micromotor (JM) moving in mineral oil between two parallel electrodes; the micromotor exhibited a rapid oscillatory motion between the two electrodes, and each single moving process toward one electrode is propelled by the ICEP.[79] In addition, the asymmetric EDL could also be generated by the asymmetric shapes of these micro/nanomotors. Ni et al. developed special hybrid clusters linked with microspheres of different materials using sequential capillarity-assisted particle assembly (sCAPA).[80] Those predesigned hybrid clusters with predetermined shapes, or so-called “colloidal molecules”, exhibited different active motions including translation, circulation, and rotation powered by the asymmetric electro-hydrodynamic flows.

More recently, Lee et al.[81] developed special spherical colloids with metal patches (Figure 5A). When remotely powered by an AC electric field, these designed particles exhibited a predefined 3D helical movement along the axis of the field with a controllable speed and shape of trajectory turned by the applied field strength and path geometry. It is noteworthy that this helical motion could promote particle transport through porous materials, which could facilitate in designing novel microrobots for advanced biomedical applications.

It is noteworthy that by combining the ICEP propulsion and electro-osmotic trapping technique, Zhang et al.[82] developed a strategy to propel, confine, and collect metallodielectric Janus particles on interdigitated microelectrodes under AC electric field (Figure 5B). It is interesting to note that the horizontal and the vertical component of the electric field induced lateral electro-osmotic flows to confine Janus particles at the electrode centers and aligned and propelled the particle via ICEP, respectively. Thanks to the electro-osmosis and the ICEP caused by the asymmetric electrical polarization of the Janus particles under the AC electric field, this study provided a strategy that is not only capable to power and confine micro/nanomotors with prefabricated tracks in a contactless, on-demand manner but also is able to concentrate active micro/nanomotors at predefined locations.

In brief, electric-field-propelled micro/nanomotors have shown promising potentials due to the positioning precision as well as unsophisticated control systems. In addition, avoiding usage of toxic fuels fosters them with even wider applications. However, to secure the successful translation of the electric-propelled motors into common use, further researches are still needed to manipulate and fabricate these motor particles.

2.2.3. Magnetic Field

Recently, magnetic-propelled micro/nanomotors have received considerate attention due to their fuel-free actuation with remote
controllability and harmlessness to cells and tissues, particularly in biomedical and pharmaceutical areas. Practically, the magnetic movement could either be created by applying a magnetic-field gradient to induce the so-called magnetophoretic motion aligned in the same direction, or directed by the magnetic torque transfer induced by rotating or oscillating external magnetic fields. The former requires spatially inhomogeneous magnetic fields, and the motility and locomotion of such micro/nanomotors are strongly impacted by the characteristics of the nano/micromotors and the magnetic properties as well as the medium properties such as viscosity. The latter could be spatially propelled by both homogeneous and heterogeneous magnetic fields, but it requires flexible micro/nanomotors capable to adapt to the field vector, which constantly varies with time.

Since Dreyfus et al. developed the very first magnetically driven micromotor, numerous efforts have been made to effectively control the motion of these magnetic micro/nanomotors, particularly in motion direction and velocity. One notable example is the closed-loop magnetic control system developed by Khalil et al. to achieve a precisely point-to-point manipulation of self-propelled microjets, both in 3D space and against the flowing streams of fluids inside a microchannel with time-varying flow rates. Lately, they also presented a robust and optimal control of magnetic microparticles inside fluidic channels with time-varying flow rates by using a magnetic-based proportional-derivative (PD) control system to compensate for the time-varying flow inside the channels. In addition, they experimentally illustrated that a cluster of paramagnetic microparticles were capable to be used to achieve a noncontact micromanipulation of microbeads, leading to an accurate positioning and successful releases at the reference positions. It is interesting to note that the motion of the cluster was controlled under the impact of the magnetic field gradient to tune the pressure gradient within the vicinity of the microbeads.

More recently, numerous reported articles focused on controlling the motion of the micro/nanomotors by designing and manipulating their geometries. Yang et al. presented a new approach to synthesize a 3D magnetic tubular micromotor with single exposure of femtosecond optical vortex. They also presented a robust and optimal control of magnetic microparticles inside fluidic channels with time-varying flow rates by using a magnetic-based proportional-derivative (PD) control system to compensate for the time-varying flow inside the channels. In addition, they experimentally illustrated that a cluster of paramagnetic microparticles were capable to be used to achieve a noncontact micromanipulation of microbeads, leading to an accurate positioning and successful releases at the reference positions. It is interesting to note that the motion of the cluster was controlled under the impact of the magnetic field gradient to tune the pressure gradient within the vicinity of the microbeads.

Figure 6. Representative examples of magnetic-propelled micro/nanomotors with geometry-controlled motion. A) Schematic diagram of the 3D tubular micromotors with single exposure of femtosecond optical vortex. B) SEM images of various structures of 2D magnetic swimmers. Reproduced with permission.

of these microswimmers could be systematically controlled by manipulating their angle and geometric design. The successful motion control, together with the unconstrained choice of materials as well as the simplicity of fabrication methods, make this magnetic novel microswimmers advantageous in the potential biomedical and pharmaceutical applications.

In addition, magnetic-propelled micro/nanomotors have also attracted increasing attention in environmental remediation and have shown potential applications. By using a one-step electrospinning method, Wang et al. designed and constructed a multi-responsive walnut-like micromotor consisting of polycaprolactone (PCL), iron oxide nanoparticles, and catalase. With the presence of hydrogen peroxide fuel, the produced micromotors exhibited an autonomous movement with a controlled motion velocity under light irradiation and guided movement direction upon the application of an external magnetic field. This novel micromotor could be applied in the field of environmental remediation due to its satisfactory ability of collecting spilled oil inside a solution and then separated using the external magnetic field.

Li et al. synthesized a Pt-free temperature-responsive hydrogels-based micromachine based on the integration of
surface-imprinted technology with lotus pollens as template (Figure 7B). The obtained magnetic JMs exhibited excellent temperature-controlled recognition, adsorption and release capacities for erythromycin. Thanks to the controllable trajectory and easy recovery ability fostered by the external magnetic field, this hydrogels-based micromachine showed great potential for biomedical and water purification applications.

Magnetic field is one of the most commonly used external active mechanisms to transduce energy and engineer micro/nanomotors. It is capable to align these particles and provide directional navigation due to its own directionality. Although magnetic-propelled micro/nanomotors have attracted increasing attention and numerous reports emerged recently,[93–95] it is still early in their development, and the successful translation of these motors into common use, especially biomedical applications, remains a big challenge due to the lack of accurate fabrication method and the poor biodegradability of the magnetic materials.

2.2.4. Acoustic Field

As an innocuous approach that is easy to operate, acoustic field has been increasingly used to foster the requisite propulsion and to produce controllable manipulation of versatile micro/nanomotors.[96,97] It has been reported[98] that the asymmetric shape of the micro particles could lead to an asymmetric distribution of the acoustic pressure from the scattering of the incident acoustic waves on the particle’s surfaces, which produced the propulsion.

Practically, the motion control, especially an on-demand acceleration or deceleration of speed, can be directly manipulated by tuning the strength of the acoustic or ultrasound field. One example is the polymer multilayer tubular nanoswimmers developed by Wang and co-workers,[99] which was capable to photomechanically perforate a single-cell membrane. A controllable movement of the nanoswimmer toward the target cell was successfully accomplished by manipulating the external acoustic field. In addition, shape was also reported as an efficient approach to control the motion of such motors. One example is the biodegradable and shape-transformable rod-like liquid metal gallium nanomachine, also proposed by He and co-workers.[100] Fabricated by using a pressure–filter–template method, these nanomachines had an asymmetric and core-shell structure, in which the shell was composed of gallium oxide to stabilize the rod-like core of liquid gallium. The ultrasound-propelled motion and precise speed control came from the asymmetric structure and high density of these nanomachines.

In addition, Zhou et al.[101] fabricated novel ultrasound-activated metallic microrods and investigated their behaviors, specifically the in-plane orbiting and spinning dynamics (Figure 8A). Their experiment results reported that near the...
resonance ultrasound frequency, those metallic microrods could orbit in tight circles. On the other hand, these particles could spin around their long axes on nodal lines, in which phase-mismatched orthogonal sound waves possibly foster a viscous torque. It is interesting to note that such a torque produced the spins of the metal-dielectric Janus microspheres back and forth in an unusual “rocking chair” fashion. Those observations have provided interesting insights on the intriguing particle dynamics in resonating ultrasound and are capable to provide foundation for designing and developing more powerful and controllable micro/nanomotors with biocompatible energy sources.

Lu et al.\textsuperscript{[102]} reported an attractive acoustic topographical manipulation (ATM) method (Figure 8B), which is capable to achieve efficient and reproducible manipulation of diverse micro/nanomotors. In their study, the microparticles were trapped by the acoustically induced microstreaming forces and manipulated along a determined trajectory based on local topographic features. They reported that the moving speed and direction of the microparticles could be easily modulated by manipulating the applied voltage and frequency. Also by autonomously adjusting microparticles with diverse geometries and densities, this method was able to serve for automated maze solving without particle modification, external feedback, or adjustment of operational parameters. Those attractive abilities of topographical guidance under acoustic streaming manipulations are capable to provide diverse promising and practical applications such as biological sample isolation, autonomous micro/nanomotor transportation system, and low-volume chemical mixing.

Sabrina et al.\textsuperscript{[103]} reported that colloidal matter could be remotely manipulated by controlling their shapes with external ultrasound energy inputs. They designed and fabricated special gold microplates with twisted star shape (Figure 8C), particularly investigated their dynamic movement within the nodal plane of a uniform acoustic field at megahertz frequencies. It is interesting to note that they quantified the relationship between the rotational motion of the particles and their shapes and those reproduced observations could be explained by hydrodynamic simulations describing the steady streaming flows and ultrasonic actuation-induced particle motions. This specific study provided a promising method that can be utilized to manipulate the increasingly complex motion of the micro/nanomotors by designing the shapes of the colloids powered by an external ultrasound.

Ultrasound-propelled micro/nanomotors as intracellular protein delivery systems have attracted increasing attention due to their tremendous therapeutic potentials. Wang and co-workers\textsuperscript{[104]} reported a high-pH-responsive delivery system consisting of a gold nanowire motor with a pH-responsive polymer coating, using caspase-3 (CASP-3) as the model enzyme (Figure 8D). The applied nanomotor aimed to protect the enzyme from release as well as deactivation prior to reaching the target intracellular environment. Also the pH-responsive polymer coating could be dissolved upon entering the target cell and exposure to a higher intracellular pH, thereby directly releasing the active enzyme to the cytosol causing rapid cell apoptosis. Results of their in vitro studies indicated that such an ultrasound-propelled motion-based active delivery approach achieved remarkably high apoptosis efficiency within a significantly shorter time and with a lower amount of active enzyme compared with other control groups. This report demonstrated that ultrasound-propelled nanomotors are capable to act as a powerful intracellular delivery vehicle of active therapeutic proteins.

The motion propelled by acoustic propulsion shows tremendous benefits and versatile motion modes\textsuperscript{[105–107]} however, there are some deficiencies such as propulsion mechanism that is yet to be understood well, ultrasound setup could not be optimized,
and the behaviors of micromotors in practice are difficult to predict which could limit the widespread application of acoustic-propelled micromotors.

3. Biohybrid Micro/Nanomotors

Although tremendous progresses have been made in design and developing versatile artifical micro/nanomotors including both self-propelled ones and those propelled with external fields for environment remediation and goal detection,[108–110] developing appropriate micro/nanomachines not only possessing sufficient biocompatibility but also with desirable motion controllability within the extremely complicated environment of the biological media, still remains an ongoing challenge. Driven by huge potential biomedical applications including highly efficient targeted drug delivery, precise diagnostic and minimal invasive surgery, recently biohybrid or biomimetic micro/nanomachines (see Table 3), either with intrinsic chemotactic ability or guided with external field, have attracted considerable interest.[111]

3.1. Sperm Hybrid Micro/Nanomotors

As a reproductive cell that exists in various male species including invertebrates and the higher vertebrates, sperm always swims toward egg cells to achieve fertilization, exhibiting an excellent chemotaxis capability. Based on this, sperm hybrid micro/nanomotors have been lately developed to foster a targeted drug delivery.

Schmidt and co-workers reported[112] a hybrid micromotor (Figure 9A) by artificially motorizing the sperm cell with metal-coated polymer microhelices, which serve as motors due to potent, controllable, and nonharmful 3D motion behavior for transporting sperm cells with motion deficiencies to promote their natural function. These artificially motorized sperms are potentially promising for assisted reproduction. Xu et al.[113] developed a sperm-hybrid micromotor comprising a motile bovine sperm cell (Figure 9B) that serves as the propulsion source and drug carrier, and a 3D-printed magnetic tubular microstructure to magnetically guide the drug-loaded sperm cell to the target. Their results demonstrated that this hybrid micro/nanomotor is an efficient drug-delivery vehicle by first loading a sperm cell with an anticancer drug (doxorubicin hydrochloride), magnetically programming it to an in vitro cultured tumor sphere-oid, and finally freeing the sperm cell to deliver the drug locally. Chen et al.[114] designed and fabricated free-swimming functionalized sperm micromotors (FSFSMs, Figure 9C) loaded with nanoscale synthetic payloads via endocytosis (inset). Results indicated that those drug-loaded FSFSMs could controllably swim toward the target area guided by environmental chemical signals, showing an efficient self-propulsion and self-guided behavior in various biological and environmental media. The designed FSFSMs are capable to serve as intelligent microscale biohybrid motors, offering considerable potentials for diverse biomedical and environmental applications.

Despite encouraging success of those earlier attempts, there are still some limitations for the sperm-hybrid motors. It is very difficult to maintain the optimum sperm activity and fertilization

Table 3. Biohybrid micro/nanomotors.

| Types of biohybrid micro/nanomotors | Motor type | Propulsion source and motion control | Potential applications | Ref. |
|------------------------------------|------------|--------------------------------------|------------------------|-----|
| Sperm hybrid                       | Sperm cell with metal-coated polymer microhelices | Sperm cell and magnetotactic control | Assisted reproduction | [112] |
|                                    | Bovine sperm cell micromotors | Sperm cell and magnetotactic control | Drug delivery | [113] |
|                                    | Functionalized sperm micromotors loaded with nanoscale synthetic payloads | Sperm cell and chemotactic control | Drug delivery | [114] |
| Bacteria hybrid                    | Bacteria-driven microswimmer | Bacteria-driven and chemotactic and magnetotactic control | Drug delivery | [118] |
|                                    | Janus fiber rods | Bubble with catalase as fuel and geometries | Bacteria detection | [119] |
|                                    | Bacteria-driven spherical microbeads | Bacteria-driven and chemotactic control (size and geometries) | Cargo delivery | [120] |
| Cell hybrid                        | Red blood cell-mimicking micromotor | Ultrasound energy and magnetotactic control | Oxygen transportation | [16] |
|                                    | Platelet-camouflaged nanorobots | Magnetic propulsion and magnetotactic control | Isolation of biological threats | [124] |
|                                    | Macrophage–Mg biohybrid motors | Hydrogen bubble propulsion | Endotoxin neutralization | [125] |
|                                    | Neutrophil-based micromotors | Cell-driven and chemotactic control | Target drug delivery | [126] |
| Enzyme-propelled                   | Enzyme-powered microshell motors | Catalase-triggered bubble propulsion and chemotactic control, size | Drug delivery | [141] |
|                                    | Mesoporous silica-based nanomotors | Urease-powered and pH responsive | Target drug delivery | [142] |
|                                    | Micromotors equipped with DNA nanoswitches | Urease-powered and pH responsive | Microenvironment sensing and micromotor activity status indicator | [143] |
|                                    | Ultrasmall stomatocyte motors | Biocatalyst catalase and chemotactic control | Drug delivery | [144] |
capability through the whole process of performing tasks. Also, the single chemotaxis to the egg cells restricts the potential application of this biohybrid machines. Further studies are still necessary to modify and decorate these sperm-hybrid motors for versatile applications.

3.2. Bacteria Hybrid Micro/Nanomotors

Lately numerous efforts[115–117] have been made to develop bacteria hybrid micro/nanomotors due to the natural sensing abilities of bacteria to various environmental conditions, including chemoattractant/repellant, pH, oxygen level, temperature, and magnetic field. Such unique abilities of bacteria are considered to be prospective in guiding the motion of biohybrid microsystems for variety of potential applications, especially for the cargo delivery in the complicated biological environment.

Sitti and co-workers[118] introduced a novel bacteria-driven microswimmer (Figure 10A) made of mostly single Escherichia coli bacterium attached to the surface of drug-loaded polyelectrolyte multilayer (PEM) microparticles with embedded magnetic nanoparticles. Their results indicated that these fabricated stochastic microswimmers were able to swim with the mean speed of up to 22.5 μm s⁻¹, and could be programmed and targeted to specific cells due to their biased and directional motion under a chemoattractant gradient and a magnetic field, respectively. In addition, these developed active multifunctional bacteria-driven microswimmers are capable to perform targeted drug delivery with considerably promoted efficiency.

Li and co-workers[119] proposed (Figure 10B) a “motion-capture-lighting” strategy for visual, rapid detection of bacteria without complicated sample pretreatment, trained operators, and expensive apparatus. This specific strategy was carried out via integration of motion-enhanced capture of bacteria and capture-induced fluorescence turn-on of micromotors. Instead of using common microtubes and microparticles, they utilized micromotors of flexible Janus fiber rods (JFRs), which could offer multiple interactions with the bacterial surface with less steric hindrance. The motion of the JMs was propelled by the oxygen bubbles produced from the grafted catalase on one side of the JFRs. It is interesting to note that the aspect ratios of the JMs had big influence on their tracking trajectories and motion speed.

Zhuang et al.[120] (Figure 10C) focused on developing a mathematical model to describe the 3D motion and chemotaxis of spherical microbeads driven by multiple attached bacteria. They found that the experimental data of 3D swimming trajectories and other motility characteristics, including mean squared displacement, speed, turn angle and diffusivity, agreed with chemotaxis modeling results. They concluded that the motility and chemotaxis of the microswimmers are highly dependent on specific system parameters including the body size and geometry of the microswimmer, the number of the attached bacteria, and also the chemoattractant concentration gradient. This theoretical study provided an insightful mathematical modeling in understanding the underlying functioning mechanisms of the bacteria-driven spherical microbeads and their motility, which is helpful in guiding the design and development of better bacteria hybrid micro/nanomachines for a given application task.

Despite the extensive utilization of bacteria hybrid micro/nanomotors for drug delivery, bioimaging, and diagnosis due to their unique characteristics including rapid proliferation, genetic manipulation, and site targeting specificity, their clinical applications are still largely restricted by their low treatment
efficacies and unavoidable side effects. Cao et al.\textsuperscript{[121]} developed a set of stealth bacteria, cell membrane coated bacteria (CMCB) (Figure 10D), to eliminate those limitations of earlier developed bacteria hybrid motors such as high accumulation in normal organs, changed inherent bioactivities, and quick clearance by the macrophages. The in vivo results demonstrated that this CMCB was capable to serve as efficient tumor imaging agents and also have the potential for a variety of bacterial-mediated biomedical applications.

### 3.3. Cell Hybrid Micro/Nanomotors

Another attractive biohybrid motor with promising potential applications is the cell hybrid micro/nanomotor\textsuperscript{[122]} which is either integrated by coating the artificial motors with cell membranes or structured by using specific cell, such as red blood cell (RBC) and neutrophil, as a navigator. Both could provide efficient locomotion in the complex biofluids with protection of the micromotors against biofouling and immune clearance.

The propulsion of the cell membrane coated micromotors is either produced by the reaction between the synthetic micromotors and the media or assisted by the applied external intervention. Wang and co-workers\textsuperscript{[123]} originally fabricated a RBC membrane-coated magnesium JM, which displayed an efficient and programmed propulsion both in water and in biological (albumin-rich) media without any external fuel. Similarly with RBC, Gao et al.\textsuperscript{[16]} designed and fabricated an acoustically powered and magnetically navigated red blood cell-mimicking (RBCM) micromotor, which is able to actively transport oxygen (Figure 11A). The propulsion of the produced RBCM micromotors arose from the ultrasonic energy, whereas the motion direction was modulated by the applied external magnetic field.

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**Figure 10.** Representative examples of bacteria-hybrid micro/nanomotors. A) Schematic diagram of the bacteria-driven microswimmers based on PEM-magnetite nanoparticle microparticles attached to an \textit{E. coli} MG1655 bacterium. Reproduced with permission.\textsuperscript{[118]} Copyright 2017, American Chemical Society. B) JMs for motion-capture-lighting of bacteria. Reproduced with permission.\textsuperscript{[119]} Copyright 2017, Royal Society of Chemistry. C) An illustration of the forces and torques exerted on the spherical microbead by its attached bacteria, where the force and the motor reaction torque of each bacterium are state dependent (propulsion and chemotaxis in bacteria-driven microswimmers). Reproduced with permission.\textsuperscript{[120]} Copyright 2017, Wiley-VCH. D) Schematic illustration for the preparation of CMCB by extruding bacteria with cell membranes. Reproduced with permission.\textsuperscript{[121]} Copyright 2019, Springer Nature.
Apart from the erythrocyte, platelets, macrophages, and neutrophil cells also have been utilized to compose the biohybrid motors. Wang and co-workers\(^\text{[124]}\) fabricated a biologically interfaced nanorobot (Figure 11B) by cloaking a magnetic helical nanomotor with the plasma membrane consisting of diverse functional proteins associated with human platelets. The obtained nanomotors exhibited efficient propulsion in whole blood over long time periods with advantageous platelet-mimicking properties, including adhesion and binding to toxins and platelet-adhering pathogens, offering efficient binding and isolation of the biological threats. Zhang et al.\(^\text{[125]}\) developed and fabricated macrophage hybrid micromotors (Figure 11C) by coating the magnesium (Mg) microparticles with titanium dioxide and a poly(lysine) (PLL) layer, and attaching the macrophage cells to the outer PLL coating via electrostatic interactions. The motion of the macrophage–Mg biohybrid motors were determined by the size of the core of the Mg micromotor as well as the position of the macrophage during the attachment process. The obtained macrophage–Mg biohybrid motors not only maintained the functionality and viability of macrophage cells such as offering efficient transport of the living cells but also were capable to bind and neutralize pathogenic toxins, such as endotoxins. He and co-workers\(^\text{[126]}\) (Figure 11D) developed neutrophils-based hybrid motors by integrating mesoporous silica nanoparticles (MSNs) with high loading capability, which successfully transformed the intrinsic chemotaxis capability of the neutrophils into self-guided hybrid micromotors. It is interesting to note that they coated the MSNs with bacterial membranes derived from *E. coli* in advance by a camouflaging strategy to ensure the compatibility of neutrophil cells with drug-loaded MSNs. The resulting neutrophils-based biohybrid micromotors successfully inherited the characteristic chemotaxis capability of native neutrophils, which could effectively move along the chemoattractant gradients produced by *E. coli*. This reported camouflaging strategy is capable to construct synthetic nanoparticle-loaded biohybrid micromotors for versatile biomedical applications, particularly for the targeted drug delivery.

The biohybrids that mimic the cells have shown unique advantages such as good biocompatibility, improved and prolonged actuation and localization in biofluids, versatile drug loading and release strategies. However, some ongoing challenges, including promoted propulsion in complex biofluids with more controllable trajectory of programmed speed and directionality, still need to be addressed before their success in clinical applications.

### 3.4. Enzyme-Powered Micro/Nanomotors

Lately, biocatalytic micro/nanomotors\(^\text{[127–129]}\) driven by the enzyme catalysis have emerged as biocompatible alternatives to avoid the toxicity of those artificial micro/nanomotors with most commonly used chemical fuels. The autonomous motion of these micro/nanomotors is motivated by the biocatalytic reactions generated by the related enzymes such as catalase and urease, and is manipulated directionally and trajectoryally by further endowing the micro/nanomotors with sophisticated...
properties. Previous studies\cite{129,130} have reported that the size, shape, enzyme quantity and distribution, as well as the intrinsic enzymatic properties could play critical roles in motion control of such micro/nanomotors. Specifically, Patino and co-workers designed and developed a novel biocompatible micromotor\cite{131} powered by the biocatalytic decomposition of urea, and found that the enzyme quantity as well as distribution had a big impact on the self-propulsion of the urea-powered motors. In another study\cite{132} they not only successfully manipulated the motion direction of the motors by incorporating magnetic material within the Janus motor structure but also efficiently controlled their velocity by chemically inhibiting and reactivating the enzymatic activity. In addition, they made an in-depth research\cite{133} on the possibility of utilizing the intrinsic enzymatic properties including turnover number and conformational dynamics to modulate the motility of the micromotors. Both the molecular dynamics simulations and experimental results revealed that among the four different enzymes they selected (urease, acetylcholinesterase, glucose oxidase, and aldolase), urease and acetylcholinesterase were capable to produce active motion and displayed the highest degree of flexibility near the active site due to their higher catalytic rates. They also concluded that the conformational changes of urease are a precondition of its catalysis, which is crucial to produce self-propulsion.

In addition, the motion control could also be accomplished by design and producing proper morphologies.\cite{134,135} Wilson and co-workers reported a high-throughput design of an asymmetric hydrogel microparticle\cite{136} powered by the catalase-mediated decomposition of fuel. They found that the asymmetric shape and roughness of the surface make it possible to obtain motion with a homogeneously distributed catalyst. Their research demonstrated the possibility to control the motility of the micromotors by tuning their size, shape, and roughness.

Extensively, directional motility of the enzyme-powered micro/nanomotors could also be obtained by tuning the external environment or surrounding solute. Sen and co-workers reported a series of vesicles and liposomal protocells coated with different enzymes including catalase, urease,\cite{137} and ATPase,\cite{138,139} and they found that the autonomous movement of these micro/nanomotors could be regulated by externally imposing a substrate with proper gradient and by adjusting the enzymatic turnover rate. Also different enzymes resulted in distinct positive and negative chemotactic movement, which could be further governed by their interactions with the surrounding solute gradients.\cite{127} Controllable autonomous behavior of the micro/nanomotors in a biofluid medium or living systems would be more attractive. van Hest and co-workers\cite{140} constructed a self-regulated and temporal control of “breathing” microgel, utilizing urease to program a feedback-induced pH change and in turn to tune the parameters of the microgel such as size switch and fluorescence intensity, eventually leading to tunable autonomous properties of the microgel.

In addition, Chen et al.\cite{141} fabricated enzyme-powered microshell motors (Figure 12A) on multimetallic (Au/Ag/Au)
microshells along with the modification of catalase on its concave surface, which could trigger the decomposition of hydrogen peroxide to oxygen gas so as to produce bubble propulsion for the autonomous motion of microshell motors. It was found that the motion behavior of the microshell motors is dependent on the size of the motors and the fuel concentration. These findings provide a new strategy for the design and development of microshell motors. Llopis-Lorente et al.\textsuperscript{[142]} reported new (Figure 12B) nanomotors consisting of MSNs loaded with different cargo molecules gated with pH-responsive supramolecular nanovalves, equipped with urease enzymes which served as chemical engines. The results indicated that these nanomotors exhibited an enhanced Brownian motion in the presence of urea. It is interesting to note that this special nanomotor is capable to “sense” the environment and deliver and release the active molecules on demand in response to predefined stimuli. Patino et al.\textsuperscript{[143]} reported mesoporous silica-based urease-powered micromotors (Figure 12C) equipped with pH-responsive DNA nanoswitches, which are not only capable to sense the pH of the surrounding environment but also as indicators of the activity status of the micromotors, promoting the understanding of their performance in different media and in different applications. Wilson and co-workers\textsuperscript{[144]} developed and fabricated ultrasmall (around 150 nm) stomatocyte polymersomes (Figure 12D) encapsulated with biocatalyst catalase in the inner compartment of the nanomotor. It was found that the addition of PEG additive allowed for both shape transformation of small polymersomes into stomatocytes and encapsulation of biologics. The moving velocity of the nanomotors could be controlled by manipulating the production of O\textsubscript{2}. The resulting ultrasmall stomatocyte motors are capable to guarantee an enhanced penetration across the vasculature model and an increased uptake by HeLa cells in the presence of fuel compared with the small stomatocyte nanomotors as control groups.

3.5. Biohybrid Micro/Nanomotors with External Taxis

Although numerous reported hybrid micro/nanomotors\textsuperscript{[145]} are capable to perform versatile functionalities, the capability to miniaturize these motors has not yet accomplished the complexity and intelligence of natural molecular devices. As a result, external propulsions including light\textsuperscript{[146]} ultrasonic waves,\textsuperscript{[147]} and magnetic fields,\textsuperscript{[116,148]} are commonly imposed to precisely manipulate biomimetic micro/nanomotors.

As mentioned earlier, Khalil et al. have developed a magnetic-based actuation system for the motion control of the micro/nanomotors not only including microjets, clusters of microbeads, which has been discussed in detail in Section 2.2.3 but also involved biohybrid micro/nanomotors. One example\textsuperscript{[149]} is that they presented closed-loop control approach for the magnetotactic bacteria (MTB) to manipulate the direction and the velocity of the MTB. Specifically, the direction was tuned by orienting the magnetic fields toward the reference position, whereas the velocity was decreased by alternating the direction of the fields based on the frequency response of the MTB. In addition, they claimed that the closed-loop control characteristics depended on their self-propulsion and magnetic dipole moments, which could be further controlled through the growth conditions of the MTB.\textsuperscript{[150]} One notable advantage of null-space control system is that it successfully accomplished a point-to-point positioning of an MTB accurately and precisely. Another example,\textsuperscript{[151]} designed and developed by the same research group, is the two-tailed microrobot with the promising capability of swimming back and forth using planar flagellar propulsion at low Reynolds numbers medium. They demonstrated that the flagellated motion of the two-tailed microrobot could be reversed selectively using external magnetic field.

Next to the MTB, the concept of magnetotaxis was further explored to the magnetosperm,\textsuperscript{[152]} and achieved a satisfactory point-to-point closed-loop motion control under the influence of controlled magnetic field lines. In addition, they investigated the strategy to control the motion of the magnetosperm both at low-Reynolds number medium\textsuperscript{[153]} and in a viscous heterogeneous medium.\textsuperscript{[154]}

Practically, the noninvasive localization and control of micro-robots and microdevices\textsuperscript{[155]} with visible feedback plays a crucial role for many applications including biomedical imaging, diagnosis, tracking,\textsuperscript{[156,157]} targeted drug delivery,\textsuperscript{[158]} and blood clots clearing.\textsuperscript{[159]} Among the various localization methods, magnetic localization techniques are more promising for practical applications by minimizing the volume, energy consumption, and complexity of the necessary components. Table 4 summarizes the advantages and limitations of different motion control approaches.

4. Conclusions and Future Perspectives

Advances in “smart” micro/nanomotors, either elicited by the recent breakthroughs in synthetic chemistry, biochemistry, and engineering or inspired by the biomimetics and living materials, are enabling significant progress in the surrounding areas. A distinct set of properties of those newly developed active motors, including controllably harvesting, tunably storing and directionally releasing energy on demand, provide a tremendously promising potential in diverse applications, particularly in biological detection and isolation, targeted cargo delivery, and environmental remediation. More recently, numerous efforts have been made to control the movements and interactions of these active micro/nanomotors to make it possible for their translation to the practical use. Those efforts mainly focused on two different ways, which have been fully discussed in this review. One is self-propulsion achieved by many different approaches including bubble propulsion produced by the catalytic decomposition of fuels, self-electrophoresis with asymmetric geometries, pre-designed or self-generated surface tension gradient and through living sperms, cells, or stealth bacteria. The other is utilizing powerful external fields with light, electric, magnetic, and acoustic energy. Although the latter is capable to provide remotely controllable dynamics with a more direct and facile way due to the tunable, directional, and nondepletable abilities of these external energy compared with the self-propulsion, there is a consensus that combining two or more propulsions among would be a better choice to produce a realistic progress for their practical use.

Despite the booming prosperity, clinical or practical translation of micro/nanomotors is still impeded, largely by the following issues. First, the lack of directional navigation, particularly in...
the living systems, is the major problem in many cases. Driven by this, external energy including electric or magnetic torque is increasingly utilized to align micro/nanomotors due to their innate directionality. Second, the propulsion of the micro/nanomotors, especially those self-propelled ones, so far are still depletable, leading to an inefficient driving motility. In addition, a balance needs to be carefully achieved between the complicated structures within micro or nano scales of the predesigned active motors for their functionality and the difficulties in fabricating those complex, small, and “smart” motors in the scale up. Further studies are necessary to address those issues so as to guarantee the successful translation of these micro/nanomotors into practical applications.

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Conflict of Interest
The authors declare no conflict of interest.

Keywords
biohybrid motors, external fields, micro/nanomotors, motion control, self-propelled motors

| Table 4. Summary of the advantages and limitations of different motion-control approaches. |
|---------------------------------|---------------------------------|---------------------------------|
| Motion-control approach         | Advantages                        | Limitations                        |
| Chemotaxis                      | Precise and autonomous control; Simple way without the need of large, external control systems | Chemicals or fuels needed; Poor temporal and spatial resolution of the local chemical gradients; Short duration of chemical gradient; Extremely challenging in real time control |
| Geometries/Shapes/ Surface properties | High availability in microscale and biological system; Precise and autonomous control; Minimal strategy and ease of application | Lack of appropriate fabricating method, especially in microscale system |
| Temperature                      | Achieve light- and magnetic-induced local heating; Ease of application | Damage to biological systems |
| pH                              | pH difference in the human body; Ease of application | Indicates environmental changes |
| Phototactic control              | Rapid control and immediate response; On/off motion; Easy operation; Controllable light intensity | Limited penetration ability; Restricted to certain orientation; Safety concerns of UV light; Challenging integration of light source into microscale system, especially for biomedical applications |
| Electrotactic control            | Easily altered field strength and direction; Various electrokinetic phenomena in motion control | Invasive; Potentially producing toxic gases and inorganic ions; Causing cell lysis |
| Magnetotactic control            | Noninvasiveness; High penetration; Strong controllability; Spatiotemporal control; On/off motion | Specific component requirement; Complex and large facilities |
| Acoustic field                   | Good directionality; Strong penetrating ability; Minimal deleterious effect on a biological environment; Ease to get concentrated sound energy; On/off motion | Lack of specificity; Cavitation effect; High energy |

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