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Soft microswimmers: Material capabilities and biomedical applications

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Abstract

In the last decades, microrobotics has attracted much attention of researchers due to the unique characteristics of shapes, propulsion mechanisms, and potential applications in the biomedical field. Recently, the research of microrobots has shifted to soft microrobots owing to their softness, elasticity and reconfigurability benefiting to interact with the complex channels in the human body compared to their rigid counterparts. There is significant progress on soft microswimmers and that encourages us to review this field timely to promote the development. In this review, we mainly highlight the progress of the soft microswimmers in recent years. The materials with softness, deformability and shape-morphing characteristics are surveyed as well as biocompatibility, followed by standard fabrication methods. Additionally, the locomotion based on self-propelled and external-field-driven mechanisms has been compared and discussed. Finally, the biomedical applications in imaging, targeted drug delivery and therapy, and microsurgery are highlighted followed by addressing the perspectives.

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Introduction

Background

The concept of applying miniaturized machines which can swim freely inside the human body to help diagnose and treat diseases has attracted much attention of researchers for decades [1,2]. In 1966, the movie *Fantastic Voyage* envisioned a similar scenario in which the doctors were shrunk to microscale and took the miniaturized submarine to voyage inside a patient's body to clean up blood clot. It is fantastic scenarios to apply such miniaturized machine in *in vivo* operations in the body where complex microchannels are present everywhere. With the development of nanotechnology and propulsion methods, these tiny machines as depicted in the movie with specific functionality can be fabricated into micro-/nanoscale size, and the micro-/nanoscale robots can readily get to the hard-to-reach or inaccessible regions, enabling them great potentials in the biomedical fields [3–5].

Until now, many methods have been successfully introduced to fabricate the microrobots at micro-/nanoscale, such as template-assisted method and strain engineering. In the template-assisted fabrication method, polystyrene (PS) or silica spherical microparticles are usually used as the templates, followed by sputtering or glancing angle deposition (GLAD) [6] with Pt, Au, Ni, Co, etc. With strain engineering, rigid metal or inorganic materials with the thickness of nanometers can be rolled-up into tubular and helical microswimmers [7,8]. And annelid-worm-like structures were fabricated by deposition of Ni/Fe alloys through shadow mask onto tensile pre-strained polydimethylsiloxane (PDMS) substrate [9]. The PS or silica-based microrobots, rolled-up microrobots, and annelid-worm-like microrobots are fabricated by either solid templates, rigid metals, or inorganic materials, resulting in poor deformability. On the other hand, the microchannels in the human body are composed of cell-covered tissues, sensitive, and could be easy to be damaged by rigid parts. Such an environment requires the microswimmers to have gentle interactions with the microchannels. Attractively, the microswimmers with the characteristics of softness and elasticity can exhibit superior deformation capability and interact gently with the microchannels [10,11]. Currently, the fabrication routes to soft microswimmers have been explored, such as microfluidic technique, direct laser writing (DLW), and even biological creatures' template-assisted methods.

To adapt to the microchannels, the soft microswimmers could be endowed with active reconfigurability and passive deformability. The active reconfigurability enables the microswimmers not only smartly responsive to the external stimuli but also change their shapes. Recently, the field of shape morphing capabilities for microswimmers becomes an increasingly active area in the research community, because the reconfigurable abilities can extend the adaptability of the microswimmers. On the other hand, passive deformability enables the microswimmers deforming under the coupling of external stimuli, boundaries, and their bodies. To this end, the microswimmers usually do not require small modulus and stiffness. Considering the characteristics of microchannels, the microswimmers with extreme softness seem to have the superior advantage in the gentle interactions with the sensitive surroundings in the body. However, a question is rising: can a microswimmer with extreme softness swim freely and successfully in the biofluid? If not, what degree of softness is needed for the microswimmers? To address these problems, the specific soft materials and associated fabrication routes as well as the propulsion mechanisms should be considered, which will be summarized and discussed in this review.

With the development of micro-/nanorobotics, the research community has made great attempts to introduce these micro-/nanorobots into the biomedical fields. In a previous work, Xi and co-workers designed a rigid microtube with a shape tip, and magnetically controlled the tube to drill a hole with the diameter of several micrometers in the organic tissue for potential use in biopsy [12]. Similarly, Kagan and co-workers proposed tubular bullet-like micromachines to destroy the membrane of cancer tissue [13]. These interesting works indicate the potential use of micro-/nanomachines in minimally invasive surgery although rigid micromachines were used in the experiments. Except for the rigid micromachines, the soft counterparts have been used in biomedical fields and much progress has been made in imaging, targeted delivery and therapy, and microsurgery, which will be highlighted in the review.

Low Reynolds number and Brownian motion

It is challenging to propel the swimmers to obtain net locomotion at the micro-/nanoscale. Two important concepts need to be considered carefully before tackling the effective propulsion of microswimmers in the fluid. First, the motion in a fluid refers to an essential concept of Reynolds (R_e) number, which is represented as [14], $R_e = \rho LU/\eta$, where ρ denotes the density of fluid, L is the characteristic length of swimmer, U represents the velocity of swimmer, and η is the dynamic viscosity of fluid. As the microswimmer enters the regime of low R_e number ($R_e \ll 1$), the viscous forces dominate and inertial forces can be neglected, while the fluid behavior is described as laminar flow. Furthermore, the motion of microswimmers at low R_e numbers differs significantly from their macroscale counterparts which can rely on the inertial effect to obtain locomotion. According to *Scallop Theorem* (Purcell 1977) [14], the reciprocal motion like scallop opening its shell slowly and closing its shell fast to squirt out water cannot make a scallop obtain any net locomotion. Therefore, at low R_e numbers, the theorem suggests that symmetry-breaking is required for obtaining net locomotion and continuous conversion of energy as well.

As the swimmer's size reduces further to sub-micron or nanoscale size, another effect named Brownian motion becomes increasingly significant. Generally, the sufficiently small objects in a fluid are subject to the Brownian motion, resulting from collisions between the objects and solvent molecules. Subsequently, the miniaturized swimmers could perform a diffusive motion that highly depends on the diffusion coefficient, which can be described as translational diffusion coefficient $D = k_B T/6\pi\eta R$, where k_B is the Boltzmann coefficient, T represents the temperature, η is the dynamic viscosity of fluid, and R denotes the radius of spherical object [15]. From the expression, it can be concluded that the Brownian motion becomes severe as the system's temperature increases and the object's size decreases. The importance of Brownian motion can be determined by Peclet number [15], $P_e = \nu L_1/D$, where v is the speed of self-propulsion motion, L_1 denotes the characteristic length of diffusive movement, and D represents the diffusion coefficient. In other words, the Peclet number describes the ratio of propulsion movement over diffusion movement for a given time scale. It tells us that the diffusion movement dominates for small P_e and the propulsion movement dominates for large P_e. Due to the Brownian motion, the motile directions can occur randomly, especially for objects with a size below several micrometers [15]. Hence, this kind of micro-/nanoswimmers must overcome the Brownian motion to acquire directionality.

Overall, to obtain net locomotion, the microswimmers in a fluid need not only breaking the symmetry but also obtaining enough energy from their environments to overcome the effects of low R_e number and Brownian motion. With the continuous energy and symmetry-breaking, the microswimmers can be actuated and propelled, and thereby reach the designated regions. In addition, the softness plays important role in the locomotion of the microswimmers. A microswimmer with extreme softness cannot sustain the shape in the fluid because of the Brownian motion effect, and cannot obtain enough locomotion at low R_e numbers either. From the perspective of propulsion, the softness of microswimmers also needs to be adjusted accordingly in the design and fabrication process.

Scope of the review

In this review, the recent advances in soft microswimmers have been mainly surveyed emphasizing on soft and reconfigurable materials, fabrication methods, propulsion, and biomedical applications. The soft materials are firstly discussed together with biocompatibility and biodegradability. Next, the fabrication methods of soft microswimmers including microfluidic technology, DLW, and template-assisted methods, are highlighted. To address the effects induced by low-R_e-number and Brownian motion, propulsion mechanisms are mainly summarized, followed by some representative demonstrations of shape-changing behaviors in the field of microrobotics. After surveying the material capability, the recent progress in biomedical applications such as imaging, targeted drug delivery and therapy, diagnosis and sensing, and minimally invasive surgery is highlighted. Finally, we conclude the recent advances in soft microswimmers and address perspectives on this field.

Materials for soft microswimmers

To design artificial microswimmers, two aspects should be considered at the beginning, including appearance design and structure design. The microswimmer can appear in spheres, helical swimmers, and other shapes. And the structure of microswimmers can be classified into rigid and soft. Among them, rigid microswimmers have been extensively investigated and significant progress has been made in the last decades [16]. Recently, the investigations of microswimmer have shifted to soft microswimmers [1,17]. Compared to rigid microswimmers, the soft microswimmers can deform easily and interface gently with the surroundings of microchannels in the body, showing overwhelming advantages in biomedical applications. To achieve the required deformability, the microswimmers commonly require soft materials. Besides the softness, the characteristics of biocompatibility and biodegradability should also be considered for their potential uses in biomedical fields.

Soft materials

Young's modulus is used to characterize the stiffness of solid material by comparing its stress and strain. Unlike the rigid counterparts of most inorganic materials with the modulus range of 10^4–10^9 Pa [17], some organic materials have soft attributes, showing relatively low modulus and stiffness. Such characteristics enable the microswimmers easy deformability through the coupling of their body and boundary. Therefore, to endow microswimmers with softness, the soft organic material is deemed as a promising candidate, even though the microswimmers made of rigid inorganic materials were observed to pass through a curved narrow channel due to enough elasticity of nanomembranes [18]. This section mainly focuses on soft polymers and soft biological materials.

Among the soft polymers, hydrogels are the popular ones, whose three-dimension (3D) network structure is physically or chemically crosslinked by hydrophilic monomers that can be extensively swollen in water [19]. Some hydrogel-based materials, such as hydrogel gelatin methacryloyl (GelMA) [10,20], pentaerythriotol triacrylate (PETA) [21], poly(N-isopropylacrylamide) (PNIPAM) [22], etc., are widely used in fabrication of soft microswimmers. For instance, Zhu and co-workers designed and fabricated microcapsule robots made of hydrolyzed hydrophobic poly(-methacrylic anhydride) [23]. And similar hydrogel-based Janus microcapsules coated with Ti/Pt were fabricated by Liu and co-workers for water purification [24]. Chen et al. applied a dispersed water phase including Ag nanoparticles and a photocurable ethoxylated trimethylolpropane tri-acrylate (ETPTA) oil phase containing Fe_3O_4 nanoparticles to prepare assembled Janus microparticles [25]. Similarly, Ren's group used poly(ETPTA) containing Fe_3O_4 and MnO_2 nanoparticles to fabricate assembled Janus micromotors [26]. Keller et al. prepared soft microswimmers by using poly(ethylene glycol) diacrylate (PEGDA) and dextran [27]. Moreover, lipophilic-hydrophilic micromotors were made by co-injecting inner immiscible flows consisting of lipophilic 1, 6-Hexanediol diacrylate (HDDA) and hydrophilic PEGDA into outer silicone oil, followed by photopolymerization [28]. Mei's group also used polyvinyl acetate (PVA) and PEGDA to fabricate soft helical microswimmers through microfluidic spinning [29]. Besides the hydrogels, other polymers, such as poly (vinylidene fluoride) (PVDF) [11], and elastomer [30], were also used as matrix materials for soft robots. Polymer thin films fabricated using standard lithography methods can be applied to construct flexible microswimmers responsive to changes in pH and temperature [31]. These polymers enrich the material choices in fabricating soft microswimmers.

Except for the synthesized compounds, some natural materials derived from nature creatures, such as bacterial [32], microalgal [33,34], and xylems [35], can be utilized as matrices or templates to synthesize the soft microswimmers as well, which shows superior biocompatibility and biodegradability, suggesting another promising candidate for the soft microswimmers.

Biocompatibility and biodegradability

Although the softness endows the microswimmers with easy deformability, not all soft polymers are biocompatible for biomedical uses. Therefore, the characteristics of biocompatibility and biodegradability should also be considered in the design stage, especially when microscale machines tend to be applied in the biomedical fields. Biodegradable materials consist of metals (e.g. Mg, Zn, Al), inorganic materials (e.g. SiO_2, $CaCO_3$, TiO_2, Fe_3O_4), and organic materials (e.g. some hydrogels, proteins, enzymes, plants, cells, tissues) [17,36]. Generally, biodegradable materials benefit biomedical applications because they can degrade in the bio-environments without retrieval of the microswimmers after the tasks are fulfilled. For instance, biocompatible components such as magnetite decorated cells with DNA-stranded flagella microswimmers were first designed and fabricated in 2005 by Dreyfus and co-workers [37]. Similarly, biodegradable magnetite nanoparticles mixed with poly(ethyleneglycol) diacrylate (PETDA) and PETA were also used to fabricate helical microswimmers [21]. Compared to the polymers and biodegradable magnetic nanoparticles, the biological components have superior attributes in biocompatibility. Some bacterial, such as bioengineered *Escherichia coli*, *Serratia marcescens*, and *Salmonella typhimurium* [5], show autologous advantages in deformability, biocompatibility, and biodegradability over synthetic cargo-carrier materials. Moreover, some plants are also deemed as promising candidates for the use in biomedical field [33,38].

Reconfigurable materials

Reconfigurable materials are not only simply to integrate soft matters into the body of microswimmers, but also adaptable and changeable shapes when they are exposed to stimuli. The materials with shape-changing properties can be mainly divided into three groups: shape memory alloys (SMA), shape memory polymers (SMP) and shape memory composites (SMC). Ni−Ti alloys, a typical SMA, reveal high rigidity and stress at high temperature and low rigidity and stress at low temperature. With appropriately heating, Ni−Ti alloys occur phase change from martensitic structure to austenitic structure, showing shape changes. SMP is usually named smart polymers, which can be in response to the physical or chemical stimuli. The hydrogels show shape-changing capabilities in the environments to response to the humidity, temperature, pH, and other stimuli [19,39]. The smart hydrogels become active field in the microswimmers. SMC is a kind of materials combining SMA and polymers, enabling shape changing.

Besides, to design the composites with shape-changing properties, other functional materials are introduced into the polymers. For instance, magnetic phase transition materials (e.g. Ni−Mn-Ga) show magnetization change depending on the temperature, which can be used in the heat transferring field. The magnetostrictive materials (e.g. Fe−Ga, Tb-Dy-Fe) can reveal very small shape changes under the stimuli of the magnetic field, which can generate a mechanical strain. And the magnetic materials, such as magnetite and NdFeB, are extensively used for magnetic field-induced shape-changing [30,40]. With the reconfigurable materials and appropriate surface decoration, the microswimmers are believed to have advantages in adaptability and changeability when carrying out missions in biomedical use, and this field is supposed to be a promising tendency in the micro-/nanorobotics.

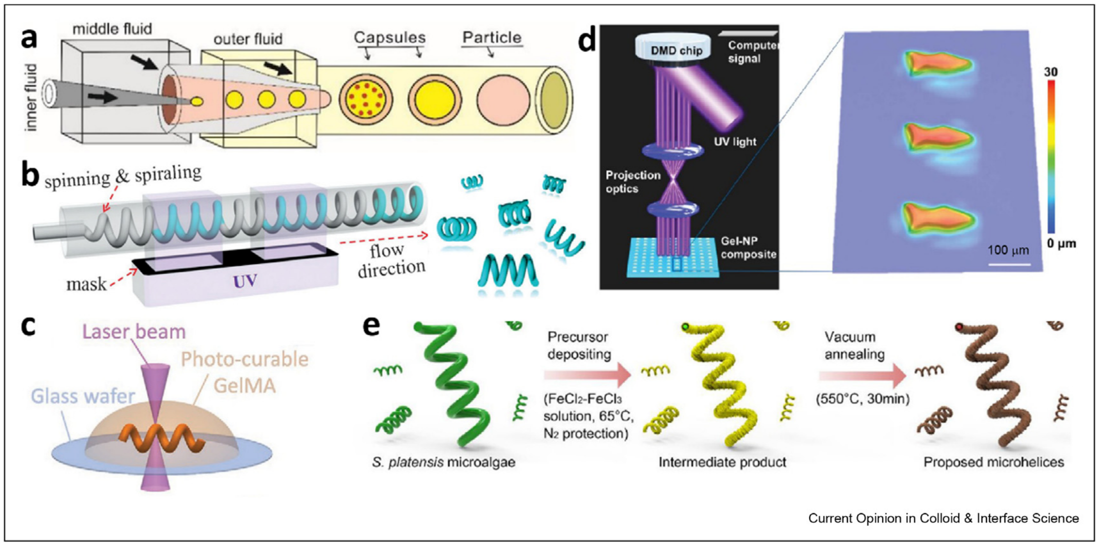
Design and fabrication

Once the soft and reconfigurable materials are chosen, the next step moves to how to fabricate the swimmers at micro-/nanoscale. Although many methods have been introduced to fabricate soft microswimmers, there are still challenges in a precise, large-scale, and economical fabrication. To this purpose, different approaches have been developed to prepare the soft microswimmers, and thereby a wide range of geometries of microswimmers can be acquired, such as spherical, helical, and other complex appearances. For instance, the helical microswimmers inspired by some flagellated bacterial, which can propel themselves by rotating their helical tails, can mimic bacterial flagella to obtain net locomotion in a liquid and adapt to the narrow microchannels [41]. Earlier works demonstrated that rolling-up pre-strained inorganic nanomembranes [16], and membrane-assisted electrodeposition [42] can be utilized for fabricating rigid helical microswimmers. However, the rolled-up technology seems not appropriate for fabricating soft microswimmers made of soft materials. Hence, this section mainly emphasizes on the fabrication methods compatible with soft microswimmers, such as microfluidic technology, DLW, and bio-template synthesis [17,36,43].

Microfluidic technology

Microfluidics is a technology based on precisely controlling the multiple phases of fluids in constrained and integrated microchannel systems [43,44]. Compared to the template-assisted methods using PS or silica spheres, the microfluidic technique with the absence of templates shows an advantage in fabricating soft microswimmers, especially the ones composed of soft organic materials. Typically, the microfluidic device consists of two thermally pulled, polished, and tapered cylindrical capillaries immersed in opposite ends of a larger square glass capillary (Figure 1a) [23]. The inner dispersed fluid phase is injected into the middle continuous phase to form discrete droplet due to the surface tension between inner and middle fluids, and then capsuled by the outer phase to form capsule-microswimmers. With a similar method, the soft colloidal microswimmers can be fabricated. The colloidal microswimmers include Janus structures and those with anisotropic microstructures [25,43], in which Janus structure consists of two

Figure 1



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Fabrication routes to soft microswimmers. (**a**) Schematic image of a glass capillary-based microfluidic device. Inner, middle, and outer flows are used for the generation of hydrogel microcapsules based on water-in-oil-in-water double emulsion drops. Reprinted from Ref. [23]. (**b**) Microfluidic spinning and spiraling method for fabrication of helical microswimmers through mask by UV. Reprinted from Ref. [44]. (**c**) Direct laser writing method for fabrication of helical microswimmers through two-photon laser beams. Reprinted from Ref. [10]. (**d**) Micro-fish microswimmer with printing method. Left image schematically shows the set-up of illustration to fabricate micro-fish. Right image shows the 3D printed fish array. Reprinted from Ref. [47]. (**e**) Microalgae-templated method for fabrication of helical microswimmers through the process of deposition and annealing. Reprinted from Ref. [48].

hemispheres with different physical or chemical properties, while in the anisotropic microstructure active hemisphere for propulsion is not designed to be even to the inert side. However, the fabrication of a microbubble with a diameter below 10 μm (i.e. below the smallest capillary in the body) is crucial to avoid gas embolism. It was proven that microbubbles stabilized by an amphiphilic protein oleosin were scaled down to 3.5 μm diameters by using a mechanically pressurized valve, which controls the diameter of the orifice in the microfluidic flow-focusing device [45].

The microfluidic technology can also be used in fabricating helical structures. Based on the injection of co-flows in the microchannels, the microfluidic spinning and spiraling system integrated with fast lithography offer an approach to fabricate helical microswimmers (Figure 1b) [43,44]. Specifically, inner fluid composed of PEGDA and Na-alginate are co-injected at precisely controlled rates into a continuous phase made of calcium chloride ($CaCl_2$) solution, and the gelation reaction between Na-alginate mixed PEGDA and $CaCl_2$ solution will occur. Due to the immediate gelation reaction and unbalanced fluidic friction between the injection flow and its surrounding fluid, continuous spiraled microfibers are obtained. The continuous microfibers will be separated by unpolymerized and polymerized parts through a specific photomask when exposed to ultraviolet lights by integrating selective lithography. Finally, the discrete polymerized PEGDA helical microswimmers are fabricated after dissolving the unpolymerized PEGDA in developers. It is noted that the length, diameter, and helical pitch can be tuned by modulating the flow rates of the microfluidic system and illuminating the frequency of UV light. Recently, Liu and co-workers used precursors consisting of inner phase with Na-Alginate and PEGDA and outer phase with $CaCl_2$-added poly(vinyl alcohol) (PVA) solution for the microfluidic spinning and spiraling system, and then fabricate helical microswimmers by gelation reaction, followed by dip-coating magnetic γ-Fe_2O_3 on the surfaces of microswimmers for magnetic actuation [46]. The microfluidic spinning and spiraling method benefit the fabrication of soft helical microswimmers made of soft polymers such as hydrogels. Overall, microfluidic technique is of significant importance for the generation of soft microswimmers and provides a facile, economical, and high-throughput method.

Writing, printing, and molding methods

DLW, sometimes also called two-photon lithography, is a laser lithography that can transfer 3D helical patterns to the photocurable materials on substrates through “top-down” approach and it mainly includes three steps (Figure 1c) [10]: the focus of two-photon laser beams at the exposure point for polymerization of photocurable materials, removal of unpolymerized photoresists to release helical structures, and then depositing thin metal layers (Ni, Co, etc.) or dipping other functional particles (Fe_3O_4, etc.) on the surface of helical structures. As the polymer materials like photocurable polymers are often used in two-photon polymerization, DLW technology benefits fabricating soft helical structures with different lengths, diameters, and helical pitches. With DLW, soft helical microswimmers composed of SU-8 photoresist were fabricated after polymerization, developing, drying, and deposition of Ni/Ti layer by e-beam deposition [49]. Additionally, photocurable GelMA-based hydrogel, which can be enzymatically degraded, was fabricated into helical microswimmers by two-photon lithography, followed by impregnating with composite multiferroic $CoFe_2O_4$(CFO)@$BiFeO_3$(BFO) nanoparticles on the surface of microswimmers for magnetoelectric stimuli [10] and magnetic Fe_3O_4 nanoparticles for magnetically propelling [20]. Except for helical structures, half-bullet-like shape microswimmers with inner cavities were designed and fabricated by a two-photon printing method on PEGDA hydrogel, which can be propelled in the chemical fuels with low drag forces [50]. By integration of computer-aided design (CAD) software and digital micromirror device (DMD) system with UV light, a 3D artificial micro-fish with complex structure composed of PEGDA and other functional nanoparticles was fabricated by continuous 3D printing method (Figure 1d) [47]. In another example, Wang's group introduced layer-by-layer assembly (LBL) and microcontact printing methods to prepare micromotors consisting of Schiff-based hydrogel [51], which provides another printing/writing route to fabricate microswimmers.

Besides the writing and printing routes, the molding method also provides alternative to fabricate soft swimmers. For instance, star-shaped hydrogel microswimmers are fabricated by molding method after the following procedures: addition of the mixtures of PVA, alginate (ALG), and Fe_3O_4 magnetic nanoparticles into star-shaped silicon pattern, gelation reaction in $CaCl_2$ solution and directly wiping off the excess materials on the surface of mold by using wet cotton swabs [52]. The precise mold offers a convenient method to fabricate predesignated shaped microswimmers, although the molding method may encounter the problem of releasing molding.

Template-assisted method

Soft microswimmers can be fabricated via the approach of template processing that can apply some plants or microorganisms as bio-templates to fabricate diverse and sophisticated functional helical structures. As a representative case, the microalgae with intrinsic helical structure is used to fabricate microswimmers (Figure 1e) [48], including deposition of magnetic precursors onto the microalgae, and dealing the intermediate products with annealing and reduction treatment. After that, the magnetic helical microswimmers with hollow carbon@magnetite core-shell structures are fabricated. Similarly, biocompatible *Spirulina*-templated helical microswimmers deposited or dip-coated with magnetic materials such as magnetic Fe_3O_4 nanoparticles were reported for the use of cargo delivery [38,53], while Sitti's group proposed bioengineered motile bacterial, *E. coli*, as microswimmers for cargo delivery [54]. Besides the microorganism templates, some vascular plants are also used as bio-templates for the synthesis of microswimmers. In plants, the xylem vessels are utilized to transport water and nutrients from the roots to the tops of the plants. Interestingly, the xylem vessels derived from various plants, such as *Rhaphioleopis indica*, *Agapanthus africanus*, *Cotoneaster lacteus*, *Passiflora edulis*, and *Musa acuminata* [35,55], have intrinsic biological structures with spiral structures. The microswimmers based on spiral xylem vessels usually include the following steps, mechanically stretched xylem vessels, depositing or coating functional materials, and dicing into small microswimmers with specific lengths. Fabrication technology of microswimmers based on spiral xylem vessels provides an alternative strategy to fabricate soft helical microswimmers in a biocompatible and cost-efficient way. Due to the inherent characteristics of softness and biocompatibility, the bio-templates hold great potentials in bio-applications.

Propulsion and control

At low R_e number, the microscopic swimmers need to continuously convert energy into mechanical work to achieve net locomotion in a liquid. This kind of energy can be provided by internal fields generated between swimmers and their surroundings or external fields provided outside. In other words, the microswimmers should interact with the fields either internally or externally to achieve propulsion. However, the conversion of energy cannot guarantee the net locomotion of microswimmers. Given that, a proper propulsion mechanism should be considered to drive the designed soft microswimmers.

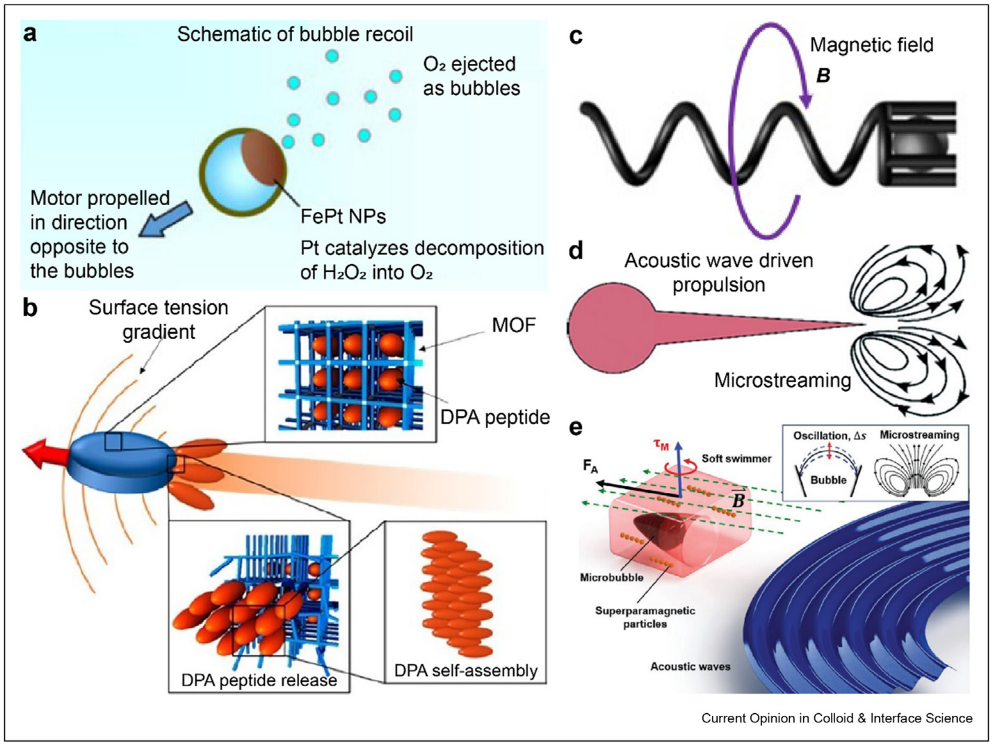
Generally, the locomotion can be achieved by imposing a gradient field or making the motile microswimmer asymmetric. Based on this, different propulsion mechanisms have been developed, mainly divided into self-propelled [39,56,57] and external field-driven mechanisms [46,58–60]. On the other hand, as the size of swimmers approaches below sub-microscale size, the movements dominated by Brownian motion become stochastic compared to microswimmers dominated by viscous forces with deterministic dynamic motion. To overcome the drawbacks of the low-R_e-number and Brownian motion, materials with specific characteristics must be evacuated carefully to actuate and propel the microswimmers. The past decade has seen increasingly rapid advances in propulsion mechanisms for artificially miniaturized machines at microscale. And currently, the shape morphing of microrobotics becomes an increasingly active area, which enables promising potential uses when the tiny machines are incorporated with reconfigurable materials. Therefore, the propulsion mechanisms of soft microswimmers and shape-changing abilities of reconfigurable materials are summarized and discussed in the section.

Self-propelling

The microswimmers can rely on themselves and their surrounding environments to achieve net locomotion, which is often called self-propulsion, and self-propulsion commonly relies on self-generated field gradient around them [56]. However, self-propulsion also comes at a cost, consuming chemical energy from the environment and converting it into mechanical motion. Usually, the microswimmers with self-propulsion mechanism obtain net locomotion via harnessing interfacial phenomena between them and their environments as inhomogeneities exist at the interface. Phoretic effects can be harnessed to propel microswimmers, such as diffusiophoresis, electrophoresis, thermophoresis, osmophoresis, and acoustophoresis [61]. Diffusiophoresis is a chemically driven propulsion mechanism, relying on the interactions between colloidal microswimmers and inhomogeneously distributed small molecules of the solute [56]. For self-electrophoresis, a built-in asymmetric structure is introduced into the bimetallic nanomotor that can move in a self-generated gradient [56]. The mechanisms of phoresis-related motion that can be found in the review literature [56,61–65] seem to be beyond the scope of the review. Therefore, in the following section, we will focus on the self-propelling mechanisms, such as bubble recoil and Marangoni stress.

The microbubble recoil mechanism relies on extruding the gases from one end of micromachines due to the decomposition of chemical fuels (e.g. H_2O_2) (Figure 2a) [66] or redox reactions [67,68]. Typically, the generated bubbles gather at the one end of micromachines, and then detach themselves after reaching the detachment radius, inducing a momentum change and thereby a driving force away from the end surface [69,70]. With the driving force, the non-zero detachment velocity of bubbles could propel the micromachines forward along the preferred direction in the fluid. In order to

Figure 2



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Propulsion mechanism of soft microswimmers. (**a**) Schematically showing the colloidal microswimmers propelled by bubble recoil (O_2) generated by decomposition of H_2O_2. Reprinted from Ref. [66]. (**b**) Schematic of MOF-based swimmer propelled by surface tension gradient. DPA peptides are incorporated into the pores of the MOF. DPA peptides are released and self-assembled at the end of the MOF particle and lower the surface tension on that side. The Marangoni effect drives the MOF particle to move toward higher surface tension. Reprinted from Ref. [57]. (**c**) Magnetic field propelled mechanism for helical microswimmer. Reprinted from Ref. [49]. (**d**) Acoustic wave propelled propulsion of soft microswimmer due to the microstreaming at the tip originating from the oscillation of the flagellated tail. Reprinted from Ref. [58]. (**e**) Magneto-acoustically propelled soft microswimmers made of microcavities at the centers of polymer matrix and aligned superparamagnetic nanoparticles. Reprinted from Ref. [86].

decompose the fuel like H_2O_2, the catalysts such as Pt [71], MnO_2 [26], and enzyme-based catalyst [27] are routinely applied. Besides the oxygen bubbles, the hydrogen (H_2) microbubbles were also used to propel the microswimmers, such as using Zn to reduce the H^+ into H_2 [70].

When utilizing the bubble recoil to propel the miniaturized machines in bio-environment, there may exist two drawbacks—toxicity of chemical fuel and maneuverability of motion. Due to the toxicity of H_2O_2 in bio-environment, some biocompatible chemical fuels are searched to drive the microswimmers. In the body, the majority is water. The idea of using water as a chemical fuel is thereby rising. Attractively, Mg, the fourth-highest element in the human body, can react moderately with water in a biofluid, propelling the microswimmer based on H_2 microbubble recoil, and reveals superior biocompatibility when being combined with biocompatible hydrogels [72—76]. Although many challenges still exist, it paves the way toward biocompatible and biodegradable approaches. Besides, trajectory motion induced by microbubble recoil has difficulty in directionality due to the gases' extrusion based on the complicated chemical reactions. To precisely control the moving trajectory, a magnetic field was usually introduced in motion control by decorating magnetic materials into the microswimmers [2,67].

Another type of self-propulsion mechanism relies on Marangoni stresses produced by the surface tension gradients at the surface. This propulsion does not rely on the built-in asymmetry like self-diffusiophoresis and self-electrophoresis but on spontaneous symmetry breaking. Marangoni stresses have attracted much attention of the scientific community due to the potential uses in propelling the robot motion at micro-/nanoscale. In 2012, Ikezoe and co-workers used metal-organic framework (MOF) as a host and diphenylalanine (DPA) peptide as a guest to fabricate DPA-MOF particles which can behave in swimming motion on the surface of ethylenediaminetetraacetate (EDTA) solution [77]. The DPA peptides were released from the pores of MOFs, and then self-assembled at the interface of water-MOF. The release and reassembly of DPA on MOFs created a hydrophobic domain with lower surface tension. Therefore, the DPA peptides modified MOF-based particles were propelled by the surface tension gradient around MOFs toward high surface tension (Figure 2b) [57,77]. The motile MOF-based swimmers have become an emerging active area for the researchers [57].

Besides the MOF-related materials, hydrogels are active, biocompatible materials, and tiny machines composed of hydrogels show the capability of autonomous locomotion on the surface of water. Inspired by striders, Zhu and co-workers designed and fabricated active hydrogel-based artificial striders, which can obtain locomotion on the surface of water propelled by the surface tension asymmetry generated by the dynamic wetting process between the hydrogel and water [39]. These hydrogels indicate potential uses in the environment field and cargo transporting applications.

External field-propelling

Although self-generated field gradients can propel the microswimmers, there exist directionality problems. The external fields, such as electric field, light, ultrasonic wave, magnetic field, and even hybrid form, can be applied to propel the microswimmers with high directionality and speed. The electric field can be applied on propelling the microswimmers consisting of dielectric materials which could generate charge distribution on the surface of swimmers due to the unstable charge distribution on the surface of the colloid when the threshold voltage is applied, which causes symmetry breaking [78]. Both alternating current (AC) and direct current (DC) electric fields can induce the locomotion of dielectric colloidal microswimmers [79,80]. Recently, Bharti's group propelled spherical particles to move along 3D trajectories under control of AC electric field [81]. Light is another field that induces the motion of microparticles in the solution via photocatalyzed reaction in the components of microswimmers. As a typical case, a photocatalytic TiO_2—Au Janus microswimmer with a diameter of about 1 μm can be propelled with TiO_2 side forward by low ultraviolet light energy in pure water without any addition of surfactants or toxic chemical fuels [82]. As the electric and light fields are used to propel rigid microswimmer made of metal or solid polymer, the propulsion fields associated with soft microswimmers, such as magnetic field, ultrasonic wave, and hybrid form, will be highlighted in the section.

The magnetic field propels the microswimmers by transforming the magnetic energy into mechanical work in magnetic torque and magnetic force. Since the low strength of the magnetic field is harmless to the organs or tissues, the magnetic field-driven microswimmers are deemed as a promising approach for *in vivo* operations. Generally, a magnetic object inside the magnetic field will be subject to two kinds of magnetic effects, magnetic force and magnetic torque [15]. The motions propelled by the two kinds of magnetic effects are described as force-driven and torque-driven mechanisms, respectively. In order to obtain a continuous motion, the magnetic field could be either spatial-varying or temporal-varying. As for spatial-varying magnetic field, a gradient magnetic field could impose a force dependent on distance and induces locomotion. Russell's group used a solenoid to generate a gradient magnetic field that can attract the magnetic liquid to pass the inner space of the solenoid [83]. In contrast to the gradient magnetic field, the temporal-varying magnetic field can keep the same value of magnetic field strength in a given space area consists of rotating, oscillating, and pulsed. Many magnetic microswimmers were demonstrated to be propelled by the above-mentioned magnetic fields [46,84]. For instance, DNA strands-linked ferromagnetic microscopic artificial swimmers obtained net locomotion due to the oscillating motion of a soft body with more than one hinge which breaks the symmetry under the externally oscillating magnetic fields [37]. Additionally, the rotation-translation coupling enables magnetic microswimmers transforming rotation into locomotion. Figure 2c depicts a magnetic microswimmer that can obtain net locomotion under rotating field due to their helical structures and transport cargos using the microholder [49]. Recently, soft micromachines consisting of hydrogels and magnetite were used to program magnetic anisotropy and morphology [22]. Similarly, Liu and co-workers applied hydrogel-based magnetic soft helical microswimmers to pass through the narrow microchannels under the rotating magnetic field [46], indicating a potential use in the human body with a harmless, biocompatible, and maneuverable manner. Interestingly, Chen and co-workers applied photocurable GelMA-based hydrogel and composite multiferroic $CoFe_2O_4$(CFO)@$BiFeO_3$(BFO) nanoparticles to fabricate soft microswimmer, which can be magnetically propelled and utilized for neuron-like cell differentiation due to the transient changes of surface charges on BFO shells induced by the magneto-strictive effect of BFO [10].

The ultrasonic wave is also found to propel the microswimmers continuously forwarding. Normally, the autonomous motion propelled by ultrasonic waves comes from the shape asymmetry induced asymmetrical acoustic pressure. As a typical example, PEGDA-based microswimmers with a flagellated tail can be acoustically propelled due to the microstreaming at the tip originating from the oscillation of the flagellated tail (Figure 2d) [58]. Recently, Sitti and co-workers developed bullet-shaped surface-slipping micromachines containing spherical air bubble trapped inside the cavity [85]. And the acoustically driven surface-slipping micromachines exhibit fast and unidirectional locomotion on both flat and curved surfaces due to the bubble inside the bullet-shaped micromachines resonated by acoustic waves and thereby fluidic flow.

The microswimmers can be not only propelled by a single form of the external source but driven by multiform power via incorporating more than one external source. As a typical example, a polymer-based soft microswimmer made of microcavities at the center of the body and aligned superparamagnetic nanoparticles can be propelled at a relatively large repulsive force under the coupling of bubble oscillation-induced force and rotating magnetic field-induced torque (Figure 2e) [86]. Similarly, magneto-acoustic powered microcapsule-shaped microswimmers composed of photoresist and Ni-coated layers were developed for single particle manipulation [87]. Additionally, as a kind of hybrid form, biological creatures can be utilized for propelling the microswimmers, such as biohybrid Janus microswimmers driven by *E. coli* [59], biohybrid microtube swimmer driven by single captured motile bacterial [60], and the like.

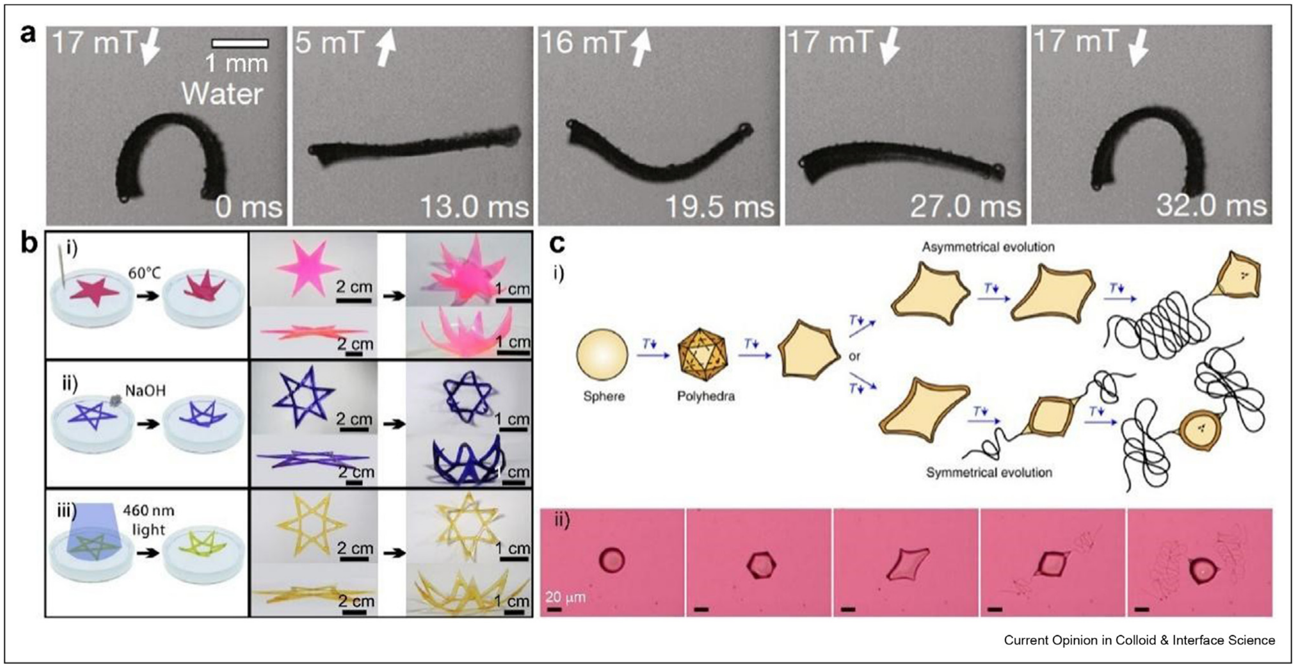
Shape changing

As mentioned previously, the softness and elasticity enable the soft microswimmers' deformability under the external stimuli. Compared to the passive deformability, the prepared structures made of reconfigurable materials can be responsive to the external stimuli actively. And the soft and smart hydrogel-based material becomes an emergingly active field in actuators, sensors, and artificial robots [39,88]. Sitti's group embedded hard magnetic NdFeB microparticles into silicone elastomer to predesign the magnetization distribution of soft microrobots. Thereby, the soft microrobot possesses shape-changing behaviors under the control of magnetic field, inducing jellyfish-like swimming in the water (Figure 3a) [30]. Similarly, Velev's group used magnetic actuation method to program 3D-printed silicone soft architectures [89] and assemble different reconfigurable shapes of magnetic microcubes [90]. Recently, Mei's group prepared hydrogel precursor and fabricated different appearances of structures by soft mold casting technology. The prepared hydrogel-based structures reveal capabilities of shape morphing under the external stimuli (e.g. temperature, pH, light, humidity, electric field) (Figure 3b) [39]. Additionally, the phase-changing capability can be harnessed to propel the microswimmers without external force. Very recently, Cholakova and co-workers applied emulsions which is prepared by alkane droplets dispersed in aqueous surfactant solution. Interestingly, the temperature changes could induce the surface phase transitions for oil droplets, with the appearance changing first and then growing thin elastic tails at cooling temperatures and retracting the tails at elevated temperatures. Fantastically, the growing and retracting thin tails can propel the droplets to obtain net locomotion in a fluid (Figure 3c) [91]. On the one hand, the small thermal oscillations of about 5 °C are enough to induce the swimmers to harness heat from the environment, resulting in growing and retracting the elastic tails multiple times. On the other hand, the mild conditions and biocompatible media endow the microswimmers with potential uses in bio-environments. This finding suggests a phase transition route to change the shape and thereby propelling the soft microswimmers.

Biomedical applications

Extensive researches on the microswimmers have been carried out to push forward the practical use in environmental applications [92] and biomedical areas [4,93]. Due to their diverse shapes with microscopic size,

Figure 3



Shape morphing behaviors. (**a**) Jellyfish-like swimming of soft robot in water via magnetic field induced shape changing. Reprinted from Ref. [30]. (**b**) Hydrogel-based structures responsive to temperature (i), pH (ii) and light (iii). Reprinted from Ref. [39]. (**c**) Shape-changing of microswimmer based on surface phase transitions under the stimuli of temperature, with (i) schematically showing the transformation of oil drop into a swimmer with one or two tails, and (ii) observed images of swimmer formed by cooling a tetradecane oil drop. Reprinted from Ref. [91].

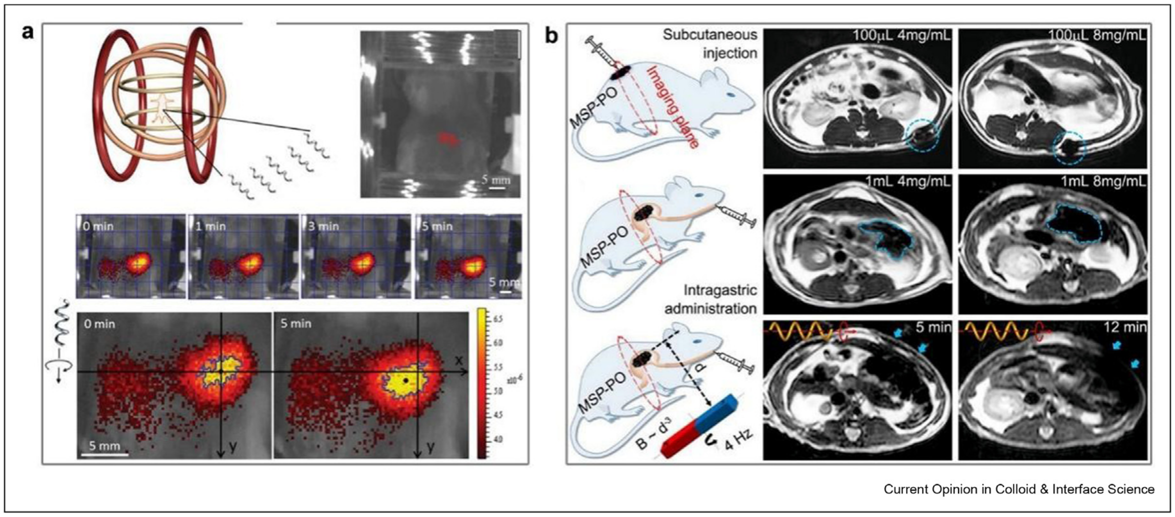
effective locomotion, and numerous propulsion power sources, soft microswimmers can reach the inaccessible regions of tissues and organs in the human body on demand with a gentle interaction manner. Such soft microswimmers hold great potential in biomedical applications. For instance, with the actuation and localization, the microswimmers can be used as imaging-assisted techniques. Furthermore, maneuverability and adaptability endow the microswimmers with potential use in the targeted drug delivery and therapy in the human body as well as diagnosis and sensing. Additionally, microswimmers are demonstrated to hold great potentials in minimally invasive surgery. Herein, recent advances in the above-mentioned biomedical uses will be highlighted and discussed.

Biomedical imaging

In biomedical use, imaging technology is valuable and essential for doctors to identify the malfunctioning tissues and organs which benefits the diagnosis and treatments. To track the location of microswimmers, the imaging-assisted techniques, such as fluorescent imaging (FI), magnetic resonance imaging (MRI), and ultrasonic imaging (USI), have been demonstrated successfully in the previous researches [94–96]. As for FI, the fluorescent signals are crucial to the technology and some materials, such as autofluorescence materials [96,97], organic dyes [98], and quantum dots (QDs) [99] that are usually used *in vivo* or *in vitro*. Steager's group developed autofluorescence materials consisting of magnetic nanoparticles and fluorescence microbeads [97]. Apart from autofluorescence materials, the organic dyes can also be used in FI. Recently, Nelson and co-workers successfully prepared soft helical microswimmers consisting of (near-infrared) NIR-979 dyes and whose body was coated with thin layers of Ni/Ti. A high amount (80,000) of Ni/Ti helical microswimmers provided sufficient signals for the tracking and FI (Figure 4a) [98]. Additionally, by decorating Janus microrobots with graphene QDs, Jurado-Sanchez and co-workers prepared magneto-catalytic microrobots to detect the endotoxin [99].

For the microswimmers propelled by the magnetic field, MRI is a very efficient method to localize the magnetic microswimmers. And the MRI can avoid the limitation of penetration of FI to detect the deep tissue. As a typical instance, biohybrid helical microswimmers decorated with magnetite were used for imaging and tracking the motion of a swarm of microswimmers [96]. The soft helical microswimmers prepared from spiral microalgal dip-coated with magnetic Fe_3O_4 nanoparticles allowed not only *in vivo* FI but also MRI of rodent stomachs (Figure 4b) in which the fluorescence-

Figure 4



Current Opinion in Colloid & Interface Science

Localization of microswimmers for the application in biomedical imaging technology. (**a**) FI based on microswimmers. Upper: The scheme of instrument of *in vivo* experiment (left) and image of an anesthetized mouse inside the magnetic coils with the red spots representing the fluorescent signal of the injected microswimmers. Middle array of images: The injected microswimmers swimming downward under the control of rotating magnetic field at different times. Bottom array of images: Magnified images from middle array of images at 0 min and 5 min, showing obvious downward swimming. Reprinted from Ref. [98]. (**b**) MRI based on microswimmers. Upper array: Magnetized *S. platensis* swarm of two different concentrations inside the subcutaneous tissues and the T_2-weighted MR images. Middle array: Magnetized *S. platensis* swarm of two different concentrations inside the stomachs and the T_2-weighted MRI. Bottom array: Magnetized *S. platensis* swarm with the same concentration but subject to actuation and steering with a rotating magnetic field before MRI across the rat's stomach. Reprinted from Ref. [96].

based imaging may suspend to work owing to its penetration limitation. Moreover, the microalgal-based microswimmers showed advantages in biocompatibility and biodegradability due to the degradation and selective cytotoxicity to cancer cells of microalgal. It was also reported that microalgal-based microswimmers were applied for photoacoustic imaging (PA) [100]. Interestingly, in nature, the magneto-bacteria consist of magnetosomes that can exhibit magnetic moments and have intrinsic biocompatible characteristics, thereby being deemed as the promising candidate for MRI [101]. Apart from the FI and MRI, the tracking of microswimmers can also be used in USI techniques which provides a low-cost, high imaging depth for human tissue [102–105]. The microswimmers with [104,105] and without microbubbles [102,103] also showed great potentials for this technology.

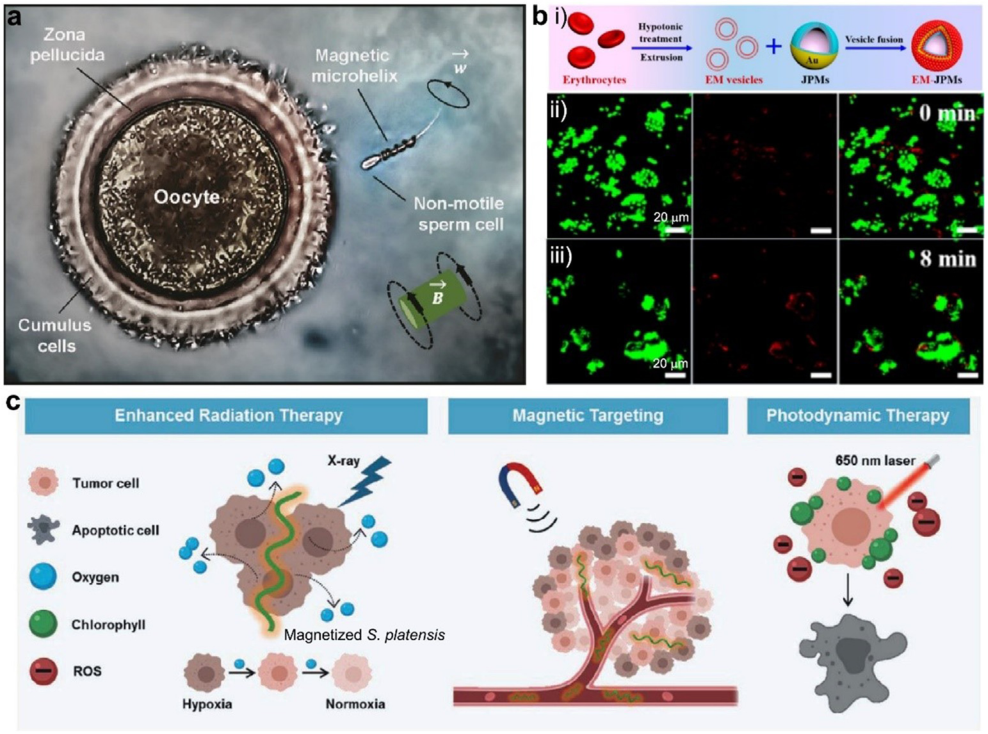
Targeted delivery and therapy

For the disease treatments, the soft microswimmers need to be propelled and arrive at the targeted regions. Interestingly, the soft helical microswimmers were utilized to transport active sperm cells to the targeted oocyte by Schmidt and co-workers. They fabricated polymer helical microswimmers coated with Ni/Ti, manipulated the microswimmers to capture and transport live sperm cells, and approach to and release from the targeted oocyte under the control of magnetic fields (Figure 5a) [106]. The artificial motorized sperm cells hold the potential use in assisted reproduction despite some challenges. The microswimmers could be also used for other disease treatments when carrying the specific cargos [107,108] and drugs, such as Ery antibacterial drug [51] and doxorubicin [109].

Thrombus is an ordinary disease of blood vessels, especially in elder citizens. As the diameters of blood capillaries are usually below several micrometers, the swimmers at micro-/nanoscale pave the way to intravascular treatments. For thrombus ablation treatments, van Hest group introduced an erythrocyte membrane-modified Janus microswimmer [3]. The Janus microswimmers with the hollow structure were prepared by sputtering a thin Au layer on the one side of polysaccharide (CHI)/glycosaminoglycan (Hep) capsuled silica templates followed by dissolving silica core. After that, erythrocyte membranes were applied for modifying the prepared Janus microswimmers (Figure 5b (i)), which can be actuated by near-infrared (NIR) due to the self-thermophoresis effect. The erythrocyte membrane-modified Janus polymeric microswimmers exhibited excellent performance in the ablation of thrombus in *in vitro* experiments in a biofriendly manner (Figure 5b (ii-iii)).

Currently, Mg nanoparticles-based miniaturized machines have been used in disease treatments, due to the moderate Mg-water reaction in the biofluid [72,74,75], and

Figure 5



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Applications of targeted delivery and therapy via microswimmers. (**a**) Assisted fertilization by sperm-carrying microswimmers with schematically illustrating a sperm is captured by a magnetic microhelix under a remotely controlled magnetic field and delivery the captured sperm to oocyte for fertilization. Reprinted from Ref. [106]. (**b**) Erythrocyte membrane-modified Janus polymeric microswimmers for thrombolysis. Upper images of (i): Schematically illustrating the modification of gold-coated Janus polymetric swimmers with an erythrocyte coating. Arrays of images from ii to iii: Time-lapsed fluorescent images of clots in the presence of Janus polymetric swimmers, showing obvious thrombolysis. Reprinted from Ref. [3]. (**c**) Schematically showing the magnetized *S. platensis*-based microswimmers for enhanced radiation therapy, tumor targeting, and photodynamic therapy. Reprinted from Ref. [95].

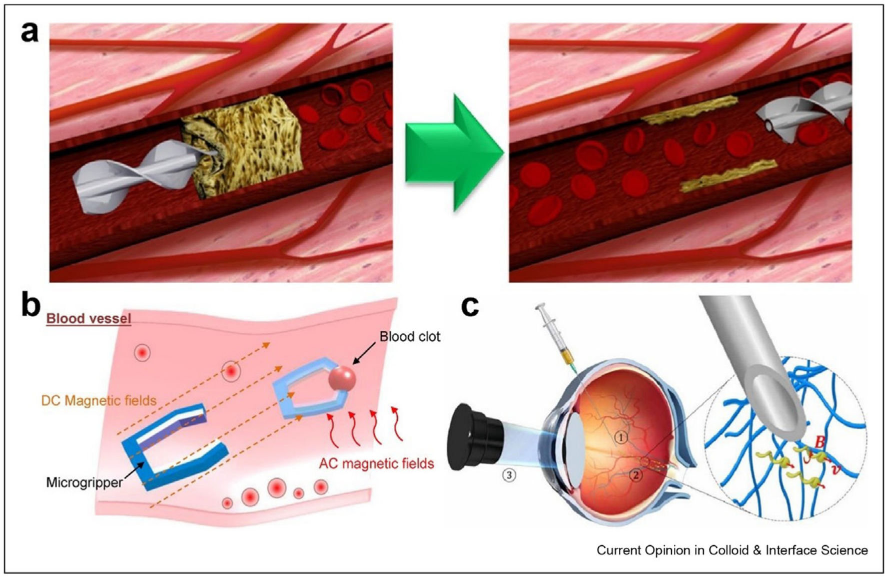
biocompatibility and biodegradability in the human body. Usually, the Mg-based matrix is covered with the biocompatible polymers to get a relative soft coating to benefit the biomedical use. Mg-based microswimmers have been demonstrated in gastric treatment via oral administration strategy [73,110] and immunotherapy [75].

In contrast to the oral delivery strategy in biomedical application, intravenous injection of the biocompatible microalgal-based microswimmers was used to treat tumor alleviation. The spiral microswimmers were prepared by *Spirulina platensis* dip-coated with superparamagnetic magnetite, which is utilized for tumor targeting and MRI, and then the magnetically engineered microalgal-based microswimmers were transferred to the tumor locations of the experimental mouse via intravenous injection (Figure 5c) [95]. The bioengineered *S. platensis*-based microswimmers can not only act as oxygen generator to improve the effectiveness of radiotherapy of hypoxic tumors via modulating the microenvironment of the tumor, but also release chlorophyll to produce cytotoxic reactive oxygen to inhibit tumors, resulting in multimodal therapies for tumors. Additionally, Wang's group applied hydrogel micromotors loaded with Pt nanoparticles and Ery antibacterial drug for injection medial, demonstrating an excellent antibacterial effect on the lesion, which offers new strategy for the treatments of bacterial infections [51].

Diagnosis and biosensing

The miniaturized machines used in biosensing have also attracted considerable attention [111] and much progress have been made by functionalizing or decorating microswimmers for diagnosis, isolation, and biosensing of DNA/RNA. For instance, the single-strand DNA decorated tubular microswimmers were exploited to capture, isolate and transport targets from raw biological samples to a designated location for subsequent analysis [112]. In the clinical area, the effective detection of microRNAs (miRNAs), regarded as a biomarker in disease diagnosis and therapy, plays a significantly important role in clinical diagnosis. However, standard methods of detecting specific miRNAs require lengthy incubation times and cell suspension with high density,

Figure 6



Current Opinion in Colloid & Interface Science

Applications of microsurgery for soft robots. (**a**) Schematic of vascular de-clogging with microrobots. Reprinted from Ref. [114]. (**b**) Schematically showing the process of hydrogel-based microrobots to swim to target region and grip the blood clot. Reprinted from Ref. [115]. (**c**) Schematic of eye-related microsurgery steps. (1) Injection of microswimmers into the vitreous humor of the eye. (2) Magnetically propelled the microswimmers in the vitreous toward the retina. (3) Observation of microswimmers at the targeted region. Reprinted from Ref. [116].

and do not allow single-cell detection. To address this problem, Wang, Zhang, and co-workers developed fluorescence-labeled single-stranded DNA (ssDNA)/graphene-oxide (GO)-coated gold nanoswimmers to detect miRNA-21, and successfully screened MCF-7 and HeLa cells due to the different expression levels of the cells [113]. Although the rigid micro-/nano-swimmers have been currently used for diagnosing and sensing in biomedical applications, these experiments provide soft microswimmers the hints of diagnosis and biosensing applications.

Microsurgery

Traditionally, minimally invasive surgery is carried out by inserting a tethered miniaturized tool from outside to the targeted locations in the body. This surgical operation is often equipped with a real-time imaging system and mechanical devices. Constricted by the size of the tethered tool, which is complicated to reduce to micro- or nanoscale, the traditional surgery hinders the practical applications in the small vessels and channels in the body. However, the untethered microscale swimmers could reach the hard-to-reach site in the body due to the microscopic size, which makes the microswimmers potential in microsurgery.

In thrombotherapy, one strategy is to dissolve thrombus by using specific chemical drugs, another way is to declog it by introducing tiny micromachines. Lee and co-workers proposed a magnetic actuated driller to clear the thrombus in the vascular network (Figure 6a) [114]. In another experiment, a soft microgripper was proposed to swim to the target region and grip blood clot directly for potential intravascular application via magnetic field control (Figure 6b) [115]. Although this microsurgery work remains at the stage of concept and many challenges need to be overcome before practical use, it suggests a fantastic application of microswimmers.

For ophthalmology, Fisher and co-workers put forward a proposal for retina therapy by injecting biocompatible helical microswimmers into the eye and propelling the microswimmers with a remotely controlled magnetic field (Figure 6c) [116]. The authors revealed that the microswimmers without coating magnetic materials remained at the positions of the dense vitreous humor not the retina after magnetic actuation. And they functionalized helical microswimmers to overcome the adhesion force in the dense vitreous humor to reach the retina for surgical operation. Besides the helical microswimmers, other shapes of micromachines such as CoNi microtubes coated with Au and PPy were also demonstrated the potential application in ophthalmology [117]. These experiments suggest that the functionalized microswimmers hold potential uses in eye-related minimally invasive surgery through an untethering manner. It is worthy to note that the timely retrieval of microswimmers after their accomplishment needs to be considered since the eye is extremely sensitive to the foreign object. Therefore, there are many challenges in the practical use of microswimmers in ophthalmology.

Conclusions and outlook

Compared to rigid microswimmers, soft microswimmers have advantages in deformability that enable the capability to access the hard-to-reach regions, and can be fabricated via economic and straightforward fabrication processes. Although tremendous efforts have been made to develop the soft microswimmers and their potential bio-applications, it is still challenging for microswimmers in practical use due to the several critical aspects in materials science, microfabrication, functionalization, actuation and propulsion, and real-time imaging system with living tissues or organisms for specific missions.

To obtain mechanical softness, organic materials with lower modulus and stiffness are usually chosen for the primary materials of microswimmers while low modulus results that microswimmers cannot maintain their geometry and get superior locomotion in low viscosity liquid [46]. Hence, appropriate modulus should be considered in the design and preparation of soft microswimmers. As for biomedical use, soft materials with the characteristic of biocompatibility and biodegradability should be considered at the stage of material choosing. Due to the inherent biocompatibility and biodegradability properties, biological materials, such as microalgal, could be promising candidates for matrix materials. For instance, using spiral microalgal as drug loading media for oral deliverable strategy seems to benefit intestinal disease treatments. And the shape-changing materials, such as hydrogel-based materials and Ni—Ti alloys, have also attracted much attention. Furthermore, some inorganic materials, such as Mg, show promising potential use in the biofield application although remaining challenges.

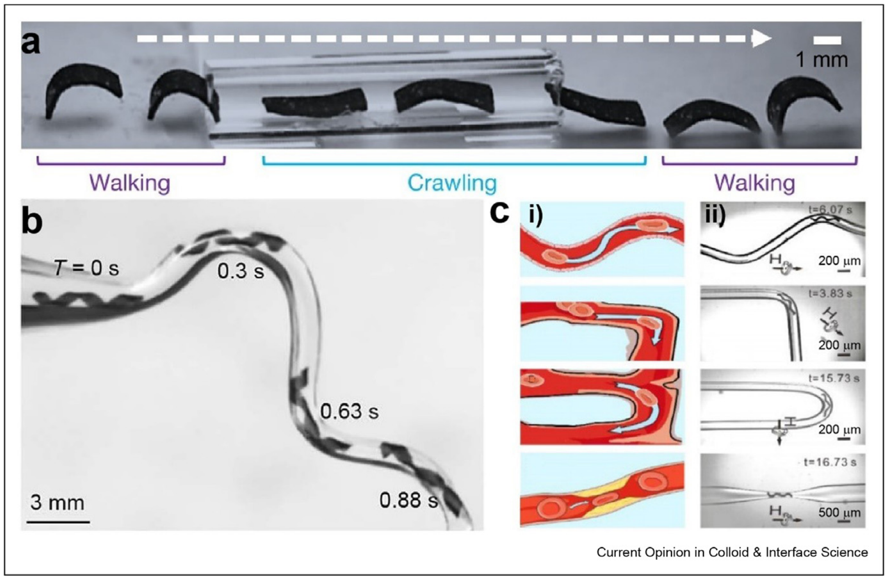
To fabricate soft microswimmers, various routes have been developed. Microfluidic technology provides a straightforward, high-throughput, and economical method to prepare colloidal and helical microswimmers with soft organic materials. However, the capillaries of microfluidic systems have to be treated by toxic chemical solvents for the hydrophobic or hydrophilic surfaces. DLW can directly print the helical and other shape microswimmers; however, the equipment with special optical source and set-up increases the cost. And there exits molding releasing problem in the molding method for soft swimmers at micro-/nanoscale. Bio-template-assisted method is considered as the economical and straightforward process to fabricate soft microswimmers. Especially, biological creatures hold superior characteristics of biocompatibility and biodegradability compared to the chemically synthesized counterparts, which indicates great potentials in biomedical applications although needing thorough *in vivo* experiments in the human body.

As objects decrease to microscale or even nanoscale size, two critical effects come to be significant, viscous effect and Brownian motion. At low R_e numbers dominated by the viscous friction, the dynamics of swimmers are deterministic and the reciprocal motion makes no difference to obtain net locomotion. Symmetry-breaking is an effective strategy to make the microswimmers obtain net locomotion. As the size of swimmers decreases further to below sub-micrometer such as self-propelled nanoswimmers, Brownian motion becomes increasingly significant, resulting in stochastic movements due to the collisions between molecules of solution and nanoswimmers. To overcome the above-mentioned two effects, careful geometry design and appropriate propulsion mechanisms should be considered. As for self-propelling mechanisms, the autonomous micro-/nanoswimmers are usually propelled depending on diffusiophoresis, electrophoresis, bubble recoil, and Marangoni stress which rely on their energy internally. It is noted that the phoresis-related mechanisms usually work on the swimmers with a size below several micrometers and motions propelled by other self-propelling mechanisms have difficulty in directionality. However, external fields (e.g. electric field, light, magnetic field, ultrasonic wave, hybrid power) drive the microswimmers to obtain net locomotion from outside, and can propel the microswimmers with directionality. The electric field usually suffers the wire connection and may not be friendly to the bio-tissues when the field exceeds a threshold; the light will provide uneven heat and cannot penetrate into objects; ultrasonic wave generates uncomfortable noise and is harmful to the other tissues, at the same time, the controllability is needed to be improved. On the other hand, the magnetic field can provide a harmless field and can penetrate the tissues or organisms, and the strength of magnetic field and narrow working space should be improved for practical use in the future.

For biomedical uses of soft microswimmers, tremendous efforts and progress have been made in the decades. Among them, the microswimmers-assisted imaging techniques, such as FI, MRI, and USI, are extensively studied. As the fluorescent signals in FI technique are usually activated by x-ray radiation, radiation could bring about harmful exposure for both the patients and surgeons. And MRI is not a real-time imaging technique and make the patients exposed to electromagnetic radiation. Although USI generates uncomfortable noise for patients, it can provide real-time imaging and safe environments for surgical operation. The imaging techniques could benefit the biomedical use of microswimmers in targeted delivery and microsurgery. It is also noted that the practical uses of microswimmers in targeted delivery and therapy and microsurgery remain challenging due to the complicated environments in the human body, safety issues, and technical problems. Although the *in vivo* diagnosis of human body with microswimmers is at the stage of concept, the point-of-care test and some other *in vitro* tests could extend the applications of microswimmers in the fields of diagnosis and biosensing.

Recently, some researches become to focus on the adaptability of soft microswimmers into the microchannels. The soft and narrow microchannels exist everywhere in the body, requiring the proper deformation capability of the microswimmers when carrying out the designated missions. The shape-changing abilities of soft materials enable soft microswimmers the ability in adapting to narrow microchannels. As a typical example, Sitti's group designed and fabricated soft millirobot via programming the magnetization distribution of robot, whose shapes can be adjusted under the control of magnetic fields, resulting in distinct motion modes, such as walking and crawling, and thereby crawling through a tubular tunnel with the diameter less than 2 mm (Figure 7a) [30]. Next, Nelson's group prepared magnetic soft helical swimmers of millimeter size that could perform enough deformation and thereby pass through narrow conduit with a diameter of several millimeters (Figure 7b) [41]. To adapt to the narrower microchannels, Mei's group reduced the size of magnetic soft microswimmers using microfluidic technology, enabled the large deformation, and successfully propelled the soft microswimmers to pass through the curved microchannels with the diameter less than 200 μm (Figure 7c) [29]. More importantly, the authors found that an appropriate softness was preferred to the soft microswimmers to pass through the narrow channels because the high modulus made the microswimmers difficult in navigating channels while the extremely low modulus rendered the microswimmers unstable to keep their shapes and non-optimized to obtain net locomotion under the magnetic field. These interesting works suggest that it is possible to use soft microswimmers in intravascular operations in the human body. Very recently, a kind of helical microrobots with deformability prepared by Ni-Ti SMAs has demonstrated the capability in unclogging the artificial clots in the microchannels, suggesting another strategy for vascular occlusion treatments [118]. It should be noted that the deformation not only takes place in the helical microswimmers, but also occurs in other shapes, such as nanomembrane folding origami [119] and Pt-PAzoMA Janus microswimmers [120], which provides other strategies for deformation. Besides the adaptive locomotion capabilities, the safety of the soft microswimmers is vital to the biomedical uses and there is a long way to put the microswimmers into real practical use *in vivo* because the current conditions in the tissues or organisms in the human body are rather complicated than those tested *in vitro*.

Figure 7



Adaptive locomotion of artificial soft swimmers. (**a**) The soft robot changes its motion mode from walking to crawling to pass through a tubular tunnel with inner diameter of less than 2 mm. Reprinted from Ref. [30]. (**b**) Optical images of an artificial soft swimmer passing through curved narrow conduit. Reprinted from Ref. [41]. (**c**) Magnetic soft microswimmers passing through different capillaries, with (i) schematic illustrations of magnetic soft microswimmers passing through sinuous, orthometric bent, U-shaped bent, and subuliform capillaries (from top to down), and (ii) optical images of passing through the corresponding capillaries. Reprinted from Ref. [29].

Although there exist limitations and challenges in the material capabilities and biomedical uses for a specific soft microswimmer, these challenges and limitations could be overcome and further advances on microrobotics could be made by the joint work of the scientific and engineering community. Herein, one possible way to promote the practical use of soft microswimmers is to utilize the advantages of soft material, fabrication, propulsion, and biomedical application to design an integrated system for intravascular application. Specifically, a kind of soft microswimmers can be fabricated by using helical microalgal as matrice loaded with thrombus ablation drugs and biocompatible magnetite nanoparticles, aiming to magnetic actuation and propulsion to the targeted regions of blood clot, and then clear clot mechanically or chemically under the real-time USI technique. There also exist other strategies to promote the development of microrobotics. And with the continuous and joint efforts of the whole scientific and engineering community, a breakthrough in micro-/nanorobotics is foreseen in the following decades.

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Author contributions

All authors contributed to the structuring and the writing of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

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