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## Mobile microrobots for bioengineering applications

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Untethered micron-scale mobile robots can navigate and non-invasively perform specific tasks inside unprecedented and hard-to-reach inner human body sites and inside enclosed organ-on-a-chip microfluidic devices with live cells. They are aimed to operate robustly and safely in complex physiological environments where they will have a transforming impact in bioengineering and healthcare. Research along this line has already demonstrated significant progress, increasing attention, and high promise over the past several years. The first-generation microrobots, which could deliver therapeutics and other cargo to targeted specific body sites, have just been started to be tested inside small animals toward clinical use. Here, we review frontline advances in design, fabrication, and testing of untethered mobile microrobots for bioengineering applications. We convey the most impactful and recent strategies in actuation, mobility, sensing, and other functional capabilities of mobile microrobots, and discuss their potential advantages and drawbacks to operate inside complex, enclosed and physiologically relevant environments. We lastly draw an outlook to provide directions in the veins of more sophisticated designs and applications, considering biodegradability, immunogenicity, mobility, sensing, and possible medical interventions in complex microenvironments.

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### Introduction

Physically intelligent material systems at the sub-millimeter scale are promising for applications in various fields, such as bioengineering (e.g., targeted therapeutics<sup>1</sup> and tissue engineering<sup>2</sup>), active matter (e.g., programmable matter<sup>3</sup> and self-organizing systems<sup>4</sup>), and microrobotics (e.g., soft

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microactuators,<sup>5</sup> mobile microrobots<sup>6</sup>). Mobile functional devices at the sub-millimeter length scales afford particular advantages to pursue novel bioengineering strategies. This size regime includes the average size of a mammalian cell, the basic building unit of a tissue or organ, thereby, permitting direct access to deep, complex, and delicate body sites, such as brain, spinal cord, heart, bile duct, pancreas, and liver.<sup>7–9</sup> Such direct access capability potentially opens up new means of medical interventions with minimal possible tissue damage compared with the tethered catheters, endoscopes, and incision-based surgery. Further, operational resolution at sub-cellular scales would allow single cell-level manipulations with high accuracy and repeatability. In the near future, this could have tremendous applications in tissue engineering and regenerative medicine; while, in the longer term, it could revolutionize the treatment of genetic diseases by single cell protein or nucleic acid delivery.<sup>6,10</sup>

Use of microrobots for lab-on-a-chip devices has already proved to be a powerful tool. Handling small objects in very small fluid volumes for manipulating, moving, and reconfiguring components in 3D by means of microrobots make this route highly attractive. Assembly of 3D heterogeneous microobjects, which require orientation and positional control, would be best addressed using microrobotic assembly.<sup>11,12</sup> Organ-on-a-chip applications could benefit from microrobotic operations, in which complex cellular materials with 3D microscale features may need to be positioned to better recapitulate the native physiological status.<sup>13</sup> Additionally, preclinical characterizations of microrobots for drug release profiles and their interactions with living tissues could be tested in organ-on-a-chip platforms.

Active and targeted delivery of therapeutic cargos, such as drugs, imaging agents, and genetic materials, are the major objectives of the first-generation microrobotic systems. Active navigation inside the body to a specific target site with a controllable cargo carrier is superior to relatively limited cargo delivery and distribution efficiencies provided by current passive routes of administrations, such as intravenous delivery and local diffusion.<sup>14</sup> Using active, drivable carriers, it is possible to minimize systemic side effects by achieving targeted local treatment options. For example, intravenously administered interleukin-12 caused lethal systemic toxicities in a clinical trial.<sup>15</sup> Active delivery and controlled on-site release schemes increase the overall bioavailability of single dose administration. Sensitive cargo types, such as proteins, peptides, or nucleic acids, are better protected from degradation inside a carrier, as they otherwise have very short half-lives in serum.<sup>16</sup> Autonomous, real-time control over cargo release dynamics would perhaps represent the state-of-the-art of the *in situ* therapeutic and diagnostic strategy. To this end, microrobots that are able to navigate inside the human body, act intelligently in response to changing conditions, carry, deliver, and release therapeutics, and perform complicated tasks in semi- or fully autonomous manners could revolutionize many clinical practices.

The first concept of miniaturized machines for bioengineering was artistically visualized in the popular science fiction movie *Fantastic Voyage* (1966). In the movie, the brain clot of a nearly dying scientist had to be removed in one hour by a submarine shrunken to microscopic size and injected into his blood stream with a small crew. In view of the scaling laws, which we discuss in the



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following section, a macroscale submarine design in the microscopic dimensions is highly inefficient to operate inside human body. However, the venture of the crew has significant overlaps with premises and vision of micro-robotics field, which constitute the main theme of the present review.

Here, we review frontline advances in the design and testing of microrobots for and toward bioengineering applications. In the following section, we provide a brief overview of micron-scale robotics and founding principles of this emerging field. We then make a higher-level classification of microrobots using on-board and off-board actuation, powering, and control approaches. We further subdivide each approach based on the mechanism of actuation/propulsion. We critically discuss design and operational capabilities of each type of microrobot in physiological environments, and provide potential pitfalls and parts to be optimized toward bioengineering applications (Table 1). In the final section, we provide an outlook toward more complex designs and applications. We

layout future challenges and critical directions to consider for rendering intelligence to microrobotic systems.

### Micron-scale robotics

A robot is by convention a reprogrammable machine with partly or fully self-contained capabilities entitled by on-board motion, perception, and learning. As a result, it can adapt to operate in complex and varying environments, and it can be programmed for different tasks. We define a microrobot in the same vein except that it has all the dimensions confined to 1 mm upper and 0.1  $\mu\text{m}$  lower limits (see *Glossary* for other definitions in the context of microrobotics).<sup>17,18</sup> Scaling physical systems down to micron scale, the significant increase in the surface-to-volume ratio, causes surface-born interactions, such as surface tension, drag, and adhesion, to become dominant compared to volumetric bulk effects, such as mass and inertia. A substantial consequence of such scaling laws is the altering mobility methods for the microrobots.

**Table 1** A brief evaluation of various microrobot designs concerning their design principles, powering and actuation schemes for generating mobility, and sensing and adaptability in the living environment

Design approach	Principal source of powering	Actuation method	Key design features for effective powering	Advantages for bioengineering applications	Major limitations
Off board (externally actuated and guided)	Magnetic fields	Rotating magnetic fields and gradient pulling	Flagellum-mimetic rigid and flexible <sup>38</sup> helices; cilia and sperm-mimetic undulating synthetic tails; <sup>42</sup> gradient pulling of magnetically active designs	Wireless powering, actuation and maneuverability; biocompatible energy source; reliable for <i>in vitro</i> , <i>in vivo</i> , and lab-on-a-chip applications	Difficulty in selective agent addressability, high cost requirements for medical instrumentation
	Acoustic fields	Acoustic radiation force and acoustic streaming	Bubble-integrated bodies; flexible tail; <sup>84</sup> microcannon; <sup>87</sup> passive particles <sup>89</sup>	Biocompatible energy source; both 2D and 3D assemblies can be realized; reliable for lab-on-a-chip and <i>in vitro</i> applications	<i>In vivo</i> use requires development of proper instrumentation; microrobot material composition and shape needs further investigation
	Light	Light-induced formation of thermal gradient around the microrobot	Generation of an air-liquid; <sup>91</sup> stable bubble encapsulation into the microrobot body <sup>100</sup>	Sub-micron resolution, multiple pathways for energy transfer ( <i>e.g.</i> , thermal, nematic alignment); can produce traveling waves; simple selective agent addressability; reliable for lab-on-a-chip and <i>in vitro</i> applications	Limited to 2D; not applicable to <i>in vivo</i> conditions; limited workspace size; requires line of sight
On board (self-propelled)	Chemical energy	Bubble propulsion	Catalytic formation of gas bubbles by breaking down fuel in a confined reactor is ejected with high speed <sup>102</sup>	High swimming speed (up to $10^3$ body lengths per second); robust power output	Toxic hydrogen peroxide is the main fuel source. High power output is possible with toxic catalyst like Pt. Action of Mg and Ni-driven systems elevate local pH
		Local chemical gradients formed around the microrobot	Asymmetric distribution of the catalyst, <i>e.g.</i> , Janus colloids <sup>113</sup>	Biocompatible fuels and catalysts, such as glucose and glucose oxidase, respectively, are possible <sup>101</sup>	Movement is extremely sensitive to the ionic strength; lack of long-range directional motion due to the Brownian effect
		Activation of cellular receptors	Physical attachment of live bacteria, sperm or muscle cells with synthetically engineered bodies <sup>27</sup>	Integrated sensing and mobility; inherently compatible with physiological fluids; comparatively high efficiency in power output	Live cells function only in delicate conditions (37 °C, 5% CO <sub>2</sub> , nutrients <i>etc.</i> ) to survive



For microrobotic swimmers in fluids, the ratio of inertial forces to the viscous drag forces, a dimensionless quantity called Reynolds number, determines the fundamental characteristics of their swimming fluid dynamics. When Reynolds number is much less than 1, viscous forces predominate inertial forces; therefore, in order for a microswimmer to propel, it has to do time-irreversible, *i.e.*, non-reciprocal, shape changes with its body.<sup>19</sup> As inertia plays an insignificant role in low Reynolds number, reciprocal motion does not lead to a displacement. In other words, the movement due to the forward component of the motion will be cancelled out by the backward component of the motion. In order to comply with such physical requirement, microorganisms have evolved elaborate swimming strategies, such as continuous rotation of helical bacterial flagella and non-reciprocal beating of a sperm tail and paramecium cilia. Such biological swimmers have already inspired a number of microswimmer designs, some of which are covered in the present review. Nevertheless, the size of the biological microswimmers tend to be limited by around 1  $\mu\text{m}$ , because molecular diffusion predominates the advection of material to the microorganisms over the active search by swimming at the sub-micron scale.<sup>20</sup> As the size of the swimmer goes down to below 0.3  $\mu\text{m}$ , the stochastic Brownian effect contributes to the most of the motion dynamics, thereby hindering long-range directional propulsion inside bulk fluid.<sup>21</sup> Below 0.1  $\mu\text{m}$ , the continuum hydrodynamics does not safely apply any longer, and the effects of quantum mechanics take over. This is the domain of nanorobotics, for which the interested readers are directed to the reviews toward this direction.<sup>22,23</sup> Altogether, understanding the scaling forces by taking into account how physical forces are experienced by entities in the lowered dimensions is a vital aspect for the design and successful operation of microrobots.

Conventionally, a robot is made to perceive and learn by means of on-board sensing and computational capabilities, so that it can decide an appropriate response in given environmental conditions. Consequently, a prime question is how this is going to be achieved at the smaller dimensions, where such computational capabilities do not exist. Programmable physical and chemical properties of microrobots, dynamically interacting with its surrounding world, sensing, and adapting to the changes in the environment can enable robust design routes for making sophisticated systems at the microscale. In nature, organisms without brains, such as slime molds, bacteria, and plants, already use physical intelligence as the main route of making decisions and adaptations to complex and evolving conditions.<sup>24–26</sup> As a result, natural systems could provide a plethora of inspiration to create similarly performing artificial miniature systems based on their physical design, processing, adaptation, reconfiguration, self-organization, and control. Early attempts toward this direction have been realized as biohybrid systems where live cells are physically integrated to artificial materials to exploit their on-board integrated powering, actuation, sensing, and control capabilities.<sup>27</sup> This concept has recently drawn a special

attention in the contexts of biohybrid microrobotics and biological soft robotics,<sup>28</sup> which will be discussed in detail later.

### Off-board approaches for microrobots

In the off-board approach, the mobility component of a microrobot is remotely actuated, powered, and steered. Other functional components, therapeutic cargo release, could still operate in an autonomous fashion based on the local signal input. Magnetic and acoustic fields are two viable sources of actuation towards bioengineering applications of microrobots, as they are mostly compatible with the living environment by safely penetrating into deep tissues. From the practical point of view, external control also brings about a direct way of controlling the microrobot inside the body. Such approach has comparatively reduced technical challenges and therefore, it has been intensely studied, and has come closer to being applicable in *in vivo* small animal testing. However, there are still unresolved issues regarding the complicated instrumentation that comes at high costs for human scales, microrobot sensory capabilities, distributed control of multiple or swarm of microrobots, limited autonomy, and so on.

**Magnetic actuation.** Magnetic actuation is a prominent remote control method for powering the microrobot mobility and spatial maneuverability. In contrast to the other alternatives, such as light and chemical signals, magnetic fields are able to penetrate biological tissues and other materials safely, which make their use for bioengineering applications highly promising. Time-varying magnetic fields and their spatial gradients provide the foundation for magnetic actuation of mobile microrobots. Under the influence of field inhomogeneity, the magnetic moment of the microrobot is attracted to the region of greater magnetic flux density, and the microrobot experiences a magnetic force.<sup>29,30</sup> As a magnetic moment in an external magnetic field experiences a magnetic restoring torque to align it with the field, a rotating magnetic field causes an unconstrained microrobot in a fluid medium to rotate. This can be exploited to generate non-reciprocal motion, which has been shown to be necessary for moving in low Reynolds numbers.<sup>31</sup> Assuming the external field is invariant, the magnetic force scales with volume of the magnetic material, *i.e.*,  $L^3$ , while the equivalent force from the magnetic torque scaling with  $L^2$ . Thus, swimming by magnetic torque-induced rotation has been preferred by researchers at smaller scales, *i.e.*, *ca.* less than 100  $\mu\text{m}$ , due to its higher efficiency. Regarding the safety, a static magnetic field under 8T is not considered dangerous for human medical use.<sup>32</sup> Nevertheless, the rate of change in gradient fields and the specific absorption rate could potentially cause tissue damage by heating. As a result, it is essential to take such safety concerns into account while optimizing the magnetic components of microrobots so as to remain within acceptable levels of magnetic field and gradient exposure set by regulatory guidelines.<sup>33</sup>

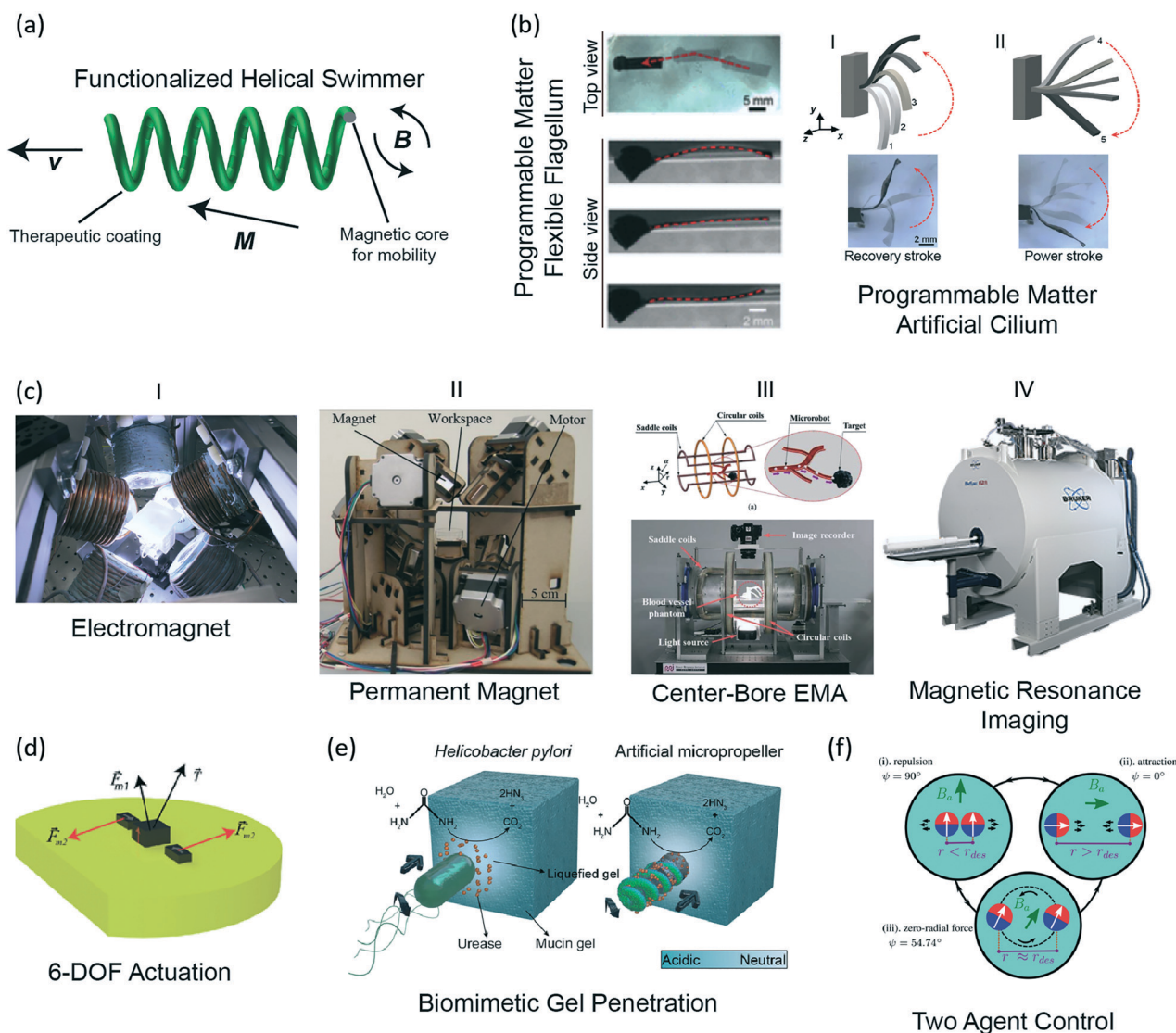
Using magnetic actuation, much design inspiration has so far arisen from the observation of bacteria, which use helical rotation of flexible flagella for propulsion, providing a



method to both propel forward and to change direction (Fig. 1a). While early research often yielded rigid artificial flagella, flexible DNA strands have also been shown to act as flagella for magnetic particles.<sup>34,35</sup> Other flexible structures have been investigated such as swimming sheets that can be controlled independently of each other<sup>36,37</sup> and rotating swimming microrobots with multiple flexible flagella.<sup>38</sup> Cellular motility structures, such as cilia and sperm-like undulations, have also served as source of inspiration for human-

engineered microswimmer mobility, as well as functional microchannel coatings that provide controlled fluid motion or mixing (Fig. 1b).<sup>39–43</sup> Propeller-shaped microswimmers can either be human-engineered<sup>21</sup> or dynamically self-assembled.<sup>44</sup> In addition, they can have multiple modalities, alternating between swimming, rolling, and propelling, depending on the substrate and control signal.<sup>45</sup>

Regarding the three-dimensional (3D) maneuverability of magnetic microrobots, 5-degrees-of-freedom (DOF) control of



**Fig. 1** Off-board magnetic actuation and powering methods for mobile microrobots. (a) Illustration of a functionalized helical swimmer, where the magnetic core is covered by a coating that can have biomedical functions, such as sensing, tissue drilling, or therapeutic drug release. (b) Programmable matter: elastomer beams, impregnated with magnetic microparticles, can be programmed to have different magnetization direction and strength locally to produce desired programmed motions, such as the undulatory motion of an artificial cilium (reprinted with permission from ref. 42. Copyright 2016 from the Proceedings of the National Academy of Sciences). (c) (i) A custom eight electromagnet coil system capable of 5- and 6-DOF control; (ii) permanent magnets mounted on stepper motors (reprinted with permission from ref. 47. Copyright 2016 from the IEEE); (iii) a four electromagnet coil system, which is capable of 3D motion control and accommodating a patient in the central bore (reprinted with permission from ref. 48. Copyright 2015 from the IEEE); (iv) a small-animal research MRI system (Bruker). (d) A body with three magnets, which create a 6-DOF controllable microrobot.<sup>46</sup> (e) A side-by-side illustration of an *H. pylori* bacterium and a synthetic swimming micropopeller, which uses a similar mechanism to penetrate the mucin gel (reprinted with permission from ref. 53. Copyright 2015 from the American Association for the Advancement of Science). (f) The basic configurations for determining separation distance using two-agent control (reprinted with permission from ref. 66. Copyright 2017 from the Springer).



microrobots was introduced by Kummer *et al.*<sup>8</sup> For an arbitrary arrangement of electromagnetic coils, they showed how to solve for the forces and rigid body torques on a single magnetic microrobot (Fig. 1ci). To avoid the need for orientation feedback, it was assumed that the microrobot had a uniform magnetization, which due to the magnetic torque, would always align with the magnetic field. Thus, only the magnetic field and magnetic gradients, which create the forces, were required to achieve the 5-DOF control. However, rotation about the magnetization axis, as the vector that aligns with the field, could not be specified. By adding known, perpendicular magnetization to a magnetic microrobot, motion about all 6-DOF was shown (Fig. 1d).<sup>46</sup> However, as this method requires careful design and feedback, 5-DOF control is still the common method in the literature. Seeking to avoid the heat and power requirements of electromagnets, a permanent magnet-based 5-DOF control system could also provide similar path-following accuracy as an electromagnet system (Fig. 1cii).<sup>47</sup> 3-DOF control is also popular as many microrobots are spherical, and thus do not require any orientation control, allowing for more design freedom, such as an electromagnet configuration which incorporates a central bore to accommodate a patient (Fig. 1ciii).<sup>48</sup>

Gradient pulling-based magnetic microswimmers carrying plasmid DNA-loaded liposomes have been demonstrated to undertake transfection of cells for selective gene editing.<sup>49</sup> A microrobot coated with a 10 nm silver layer can directly disintegrate the membrane of an *E. coli* bacterium by physical contact.<sup>50</sup> Hyperthermia induced by microrobots is a promising method to target cancer cells, without causing damage to surrounding healthy tissue. A small rod-like microrobot, rotated at sufficiently high frequencies, can feasibly generate heat from fluid drag, but has not been shown experimentally.<sup>51</sup> Alternatively, magnetotactic bacteria were shown to be able to sufficiently heat to kill *Staphylococcus* bacteria in a span of 60 minutes.<sup>52</sup> Microrobots can also be made to penetrate through some tissues by chemical assistance, such as the *Helicobacter pylori*-inspired method of using urease activity to locally degrade gastric mucin gel (Fig. 1e).<sup>53</sup>

Recent works have tackled the more difficult challenge of assembling structures and transporting cargo in 3D, which cannot be based on contact-based pushing mechanisms used in 2D. Swimming or rolling microrobots induce fluid flow by their propulsion mechanism, and can use these vortices to trap objects and transport them.<sup>54–57</sup> Flexure-based gripping mechanisms have been shown for magnetic microrobots, where the magnitude of the magnetic field is used to control the opening and closing of the gripping arms.<sup>58</sup> This was shown to be highly repeatable, assembling up to 10 layers of hydrogels around a post.<sup>12</sup> While these untethered mechanical grippers prefer parts that match the gripper geometry, microrobots with a bubble on their surfaces could pick and place a wide range of 3D and various material parts using capillary forces.<sup>11</sup>

Magnetic fields have also been used for maneuverability while alternative methods serve as the source of the mobility.

For example, 3D-printed microfish exhibit chemically powered propulsion while being magnetically guided.<sup>59</sup> Microrobots guided by magnetic fields and propelled by ultrasound were demonstrated to be simultaneously loaded with quantum dots, an anti-cancer drug, and magnetic nanoparticles.<sup>60</sup> An alternative propulsion method is the creation of fluid flows by the resonant oscillations of air bubbles within a fluid.<sup>61,62</sup> These fluid flows can additionally trap objects, and then the system can be carried by a magnetic transporter.<sup>63,64</sup>

Microrobot teams and swarms remain a critical research topic, because such an organization paves the way of parallel and distributed complex operations.<sup>65</sup> Swarm control is of particular importance as commands might be given to the whole population, subsets, individuals, or a combination of these. Control of multiple magnetic microrobots remains an ongoing topic of research, as all microrobots will receive the same global control signal. This control signal causes all microrobots to move in a coupled manner. In addition, the microrobots will either attract or repel each other due to the magnetic field gradients generated by each. By controlling the orientation of the magnets with an external field, the magnetic attraction and repulsion can be controlled to dictate the motion of the individuals (Fig. 1f).<sup>66</sup> Techniques to use non-uniformities in the field<sup>67</sup> or selective electrostatic clamps to address select individuals<sup>68,69</sup> have been shown, but require patterned and structured surfaces and environments. Even with these problems solved, interference of individual microrobots in a swarm yields a lower net velocity than a solitary swimmer.<sup>70</sup> This behavior was observed when a swarm of magnetic microrobots was driven *in vivo*, in the intra-peritoneal cavity of a mouse. However, 80 000 swimmers were required to generate a sufficient fluorescence signal to track and when coupled with the complex biological fluid medium, the mean speed decreased to  $6.8 \mu\text{m s}^{-1}$ , roughly half of the length of the microrobot body per second.<sup>70</sup>

While swarm microrobotics is promising for minimally invasive surgery, research in the functionality of individual microrobots for *in vivo* use has progressed. An artificial arterial thromboembolism was penetrated inside a live porcine model by a centimeter long microrobot using fluoroscopic imaging for position control.<sup>71</sup> Recent *in vitro* efforts have focused on improving functionality of microrobots that will eventually operate inside the body. Intra-ocular surgery is still on track to be the first use of a medical microrobot in humans, as a camera above the patient will allow for fast, non-invasive feedback of the microrobot position. Recent advancements have enhanced the mobility of microrobots in vitreous fluid and tested online measuring of the viscoelastic properties of the vitreous, vital for control optimization.<sup>9,72</sup>

The electromagnet coil systems discussed are often customized for *in vitro* research. To transition to clinical *in vivo* applications, commercial systems must either be developed or adapted from existing technologies. A magnetic resonance



imaging (MRI) device is a diagnostic tool that is utilized by most hospitals and adapting this technology could provide an affordable therapeutic modality for many clinical settings. An MRI device can both localize and actuate a micro-robot toward their clinical use (Fig. 1civ). To this end, the existing MRI devices are promising, but advances in the state-of-the-art are limited due to both the high static magnetic field and the high cost-of-entry for research. Static, multi-DOF MR-compatible devices have been developed, but mobile device control remains in its infancy.<sup>73</sup> Recent work has been able to operate such a microrobot inside a phantom with over 100 Hz feedback by limiting imaging to the direction of the applied gradients, so that all imaging sequences will yield propulsive force.<sup>74</sup> A mobile injection system has been developed in use of an MRI by using the transfer of magnetic energy in a Gauss gun configuration.<sup>75</sup> Magnetic particles can be tracked in an MRI to visualize blood vessels that are smaller than the current resolution limits of an MRI.<sup>76</sup> If the microrobot is non-magnetic, ongoing research is increasingly miniaturizing electromagnetic coils to be placed on-board a device for visualization by the MRI, though on-board miniaturized power remains an ongoing challenge.<sup>77</sup> If the object is magnetic, a new technique, dipole field navigation, was developed for tracking and actuation in an MRI. This technique allows for actuation that requires large spatial gradients, provided by a placing a magnetic sphere outside of the patient. By placing the magnet near the targeted microrobot, actuation can be achieved, and by moving the sphere with the MRI gradient coils, the MRI can automatically image and actuate the microrobot; however, optimization and *in vivo* validation and testing remain as future works.<sup>78,79</sup>

**Acoustic actuation.** Acoustic fields are another compelling source of remotely powering the microrobot mobility in controlled directions. As a technology, it is an emerging and promising field for off-board propulsion and manipulation of microrobots, while its functional design and application in a biological setting is currently insufficient and requires future developments. The physical effects of acoustic fields are mostly exploited in the forms of acoustic radiation force and acoustic streaming. Acoustic radiation force can be generated by a standing wave, which is created when a sound wave reflects back and forth in a resonator, in a biologically safe way. This creates a hydrodynamic drag force in a fluid for driving microobjects to the sound pressure nodes and antinodes, which are minimum and maximum amplitude points, respectively.<sup>80,81</sup> In this actuation scheme, the direction of motion can be predicted and dynamically altered by the corresponding wave functions. As a result, this method could be quite effective in controlling the global mobility of multiple microobjects to accumulate them in the target sites. For tissue engineering applications, in particular, this method is appealing to organize cells in 2D and 3D patterns as dense aggregates.<sup>80–82</sup> It is typically ineffective for addressing individual structures, as the acoustic fields do not have selectivity to the manipulated objects. However, application of acoustic

radiation force fields in an oscillatory fashion has recently been introduced for selective addressability. In this system, oscillating bubbles trapped within microswimmer bodies generated sufficient thrust, so using a group of microswimmers each with a unique bubble size, selective actuation of a single microswimmer from among the group was shown to be possible (Fig. 2a).<sup>62,83</sup>

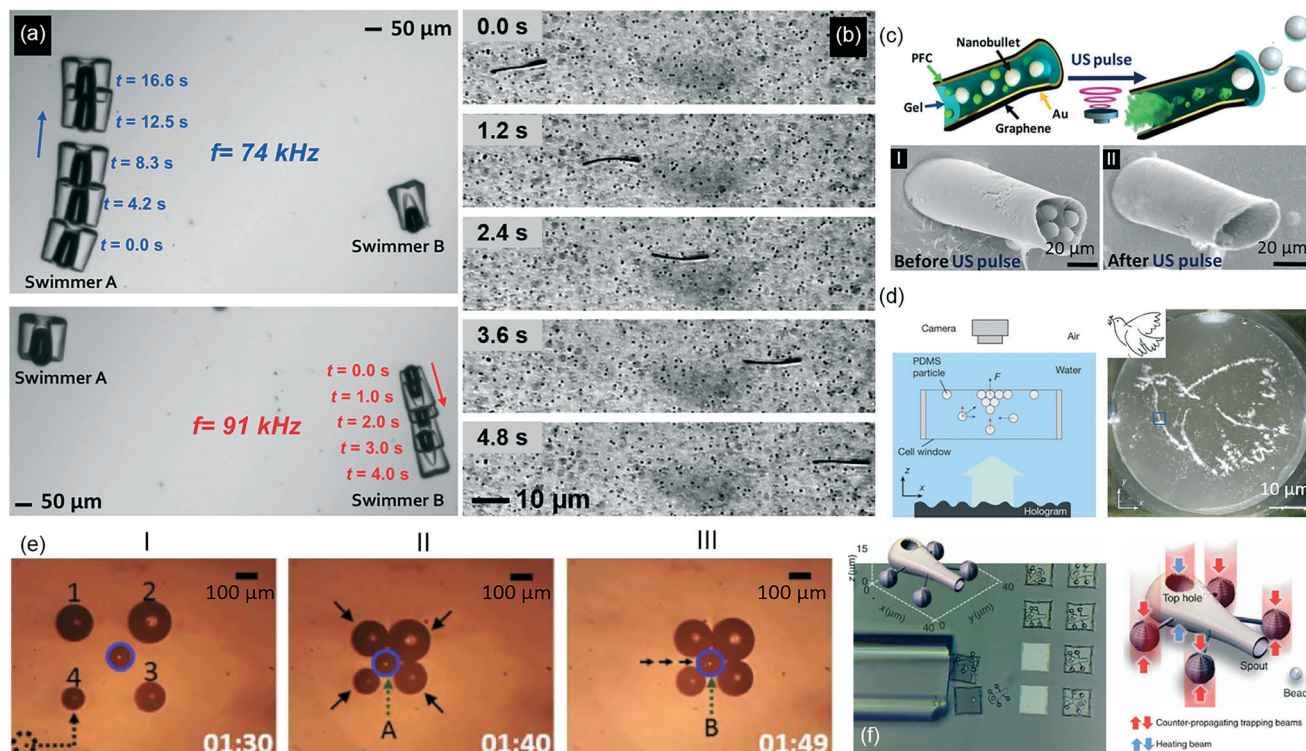
In the context of *in vivo* applications, the standing wave method is limited, because standing waves cannot be established in the human body in a predictable manner. For *in vivo* efficient propulsion, traveling wave-mediated mobility is the most advantageous strategy. In this context, an acoustically activated flagellum was recently shown to propel an artificial microswimmer through an aqueous solution by small amplitude oscillation of the tail in the presence of travelling acoustic waves (Fig. 2b).<sup>84</sup> Acoustically responsive, sperm-shaped microswimmers can also be fabricated *in situ* within a microchannel and therein actuated *via* flagella oscillation.<sup>85</sup> On the other hand, this method falls short for size scalability and maneuverability, which remain as the major improvements in the future.

Acoustic radiation force can also be generated by focusing an ultrasonic beam to physically trap an individual or a group of microobjects.<sup>86</sup> The trapped microobject can then be transferred by moving the ultrasonic transducer that generates the ultrasound. However, strong ultrasound at the focal point may cause a high temperature rise resulting in tissue damage. A noteworthy study turned this local energy buildup into advantage and proposed a potential method of drug delivery. Focused ultrasound pulse vaporized perfluorocarbon emulsion within a microcannon that resulted in rapid ejection of microparticles (Fig. 2c).<sup>87</sup> During the ejection, the speed of microparticles reached exceptionally high speeds of a few meters per second. Acoustic streaming can also generate directional propulsion force in fluids. Ultrasound actuation of a simple structure consisting of an array of comb-like cavities with trapped air bubbles oscillating at the resonant frequency of microbubbles propels the structure in the direction opposite to the acoustic streaming.<sup>88</sup>

Holographic acoustic elements have recently been introduced as a strong tool for complex manipulation of microobjects wirelessly. A remarkably simple method introduced by Fischer *et al.* demonstrated a 3D-printed surface profile used to encode the acoustic phases of the desired wavefront for enabling intricate particle patterning and trajectory control (Fig. 2d).<sup>89</sup>

**Photo (optical) actuation.** A thermal gradient across an air–liquid interface will induce fluid flow in the direction of the cooler region, due to the temperature dependent nature of surface tension. In opto-thermocapillary manipulation, the thermal gradient is generated by a focused light source, and microbubbles are manipulated as they host the air–liquid interface. In this actuation scheme, maneuverability can easily be controlled by moving the light source, thereby reforming the thermal gradient in a steady state manner. A major drawback of this, however, is that currently these





**Fig. 2** Off-board acoustic and optical actuation, powering, and control strategies for microrobots. (a) Low-power acoustic field driven oscillatory motion of a bubble enables directional motion in water. Two microswimmers with bubbles of different size enable independent control of each body (reprinted with permission from ref. 83. Copyright 2015 from Nature Publishing Group). (b) A flexible tail attached to a rigid body is actuated by travelling acoustic waves that result in directional motion (reprinted with permission from ref. 84. Copyright 2016 from the American Chemical Society). (c) Ultrasound triggered high-speed ejection of microparticle cargo from cannon-like microholes (reprinted with permission from ref. 87. Copyright 2016 from the American Chemical Society). (d) Hologram-based patterning of acoustic waves drives the assembly of microparticles into predictable reconstructions in 3D (reprinted with permission from ref. 89. Copyright 2016 from Nature Publishing Group). (e) The automated simultaneous manipulation of four heterogeneous bubbles by thermocapillary flow enables the bubbles to surround and transport a microobject (reprinted with permission from ref. 92. Copyright 2016 from the IEEE). (f) A light controlled microrobot with a particle ejecting function. By illuminating the top hole, which has a thin layer of gold for heat transduction, the resulting thermocapillary flow ejects a bead (reprinted with permission from ref. 100. Copyright 2016 from Nature Publishing Group).

setups require special substrates to transduce light into heat, and have only been demonstrated in 2D. Readers interested in recent fundamental science of thermocapillarity are referred to the literature.<sup>90</sup> Toward their application, it has been recently shown that a large number of bubbles can be generated and independently manipulated by using a liquid crystal device, which can modulate a laser wavefront into multiple outputs.<sup>91</sup> This technique has been demonstrated by an automated system to trap microobjects by surrounding them with bubbles and then pushing the object to a desired position (Fig. 2e).<sup>92</sup> Thermocapillary flow is also applicable to a liquid droplet in air. However, if the substrate were hydrophobic, the droplet would move slowly. It was shown that a lubricant layer between the droplet and substrate can increase the velocity of the flow by a factor of five.<sup>93</sup> A hybrid micromotor can use opto-thermal and chemical responses to propel through a fluid, and act as a rudimentary “logic circuit”, due to its selective responses to both light and chemicals.<sup>94</sup>

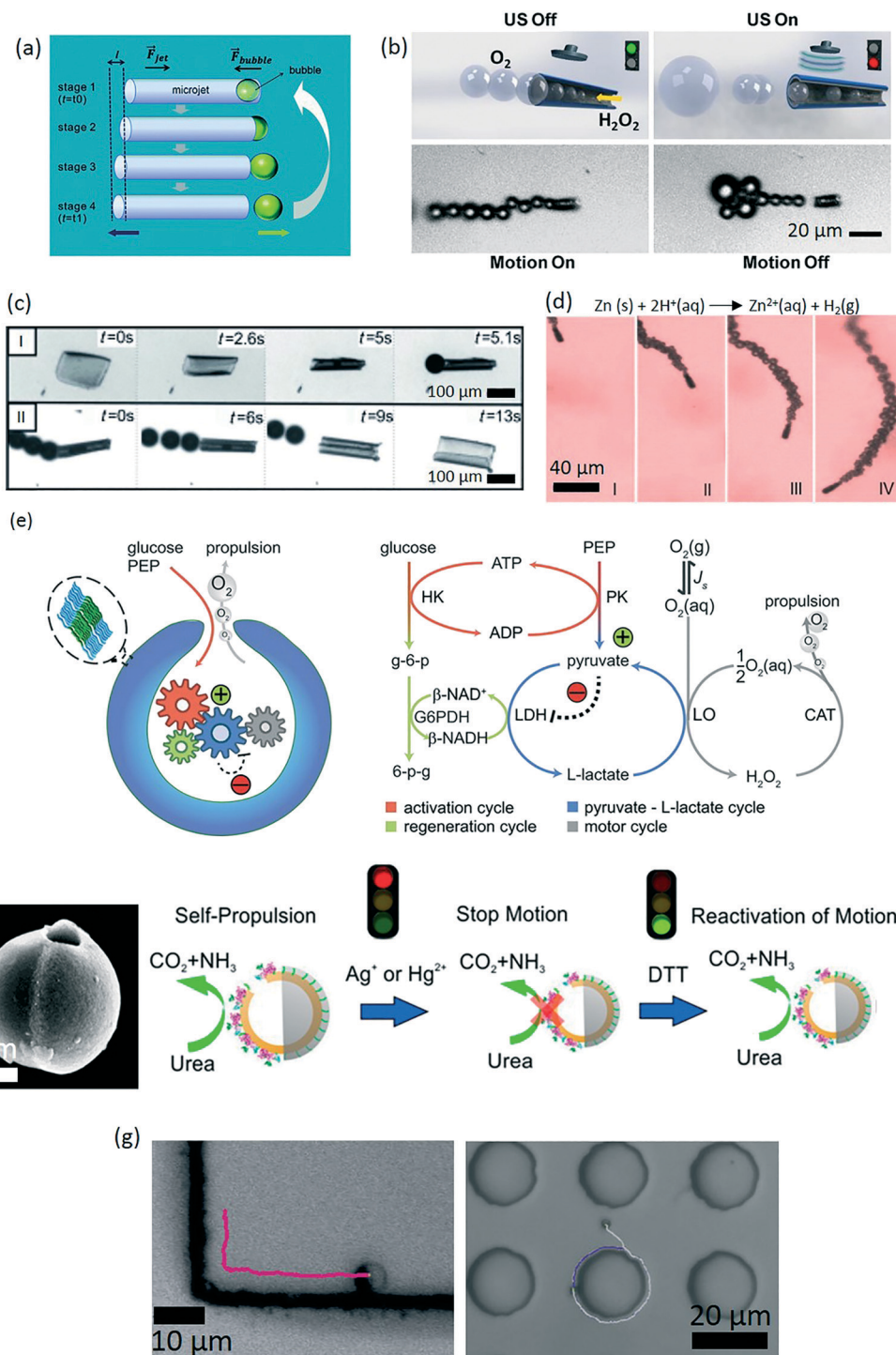
Light can also directly propel untethered microdevices. A soft device comprised of a liquid crystal elastomer exhibits

peristaltic motion under a modulated travelling light wave.<sup>95</sup> Similarly, a liquid crystalline microrobot can crawl on surfaces by contracting when heating above 100 °C and expanding with directional friction due to asymmetric legs.<sup>96</sup> This can be scaled up to a few millimeters, and by patterning the liquid crystal elastomer, the contraction can produce travelling waves in the structures, allowing the microrobot to move by propelling the wave down the length of the microrobot.<sup>97</sup> Optical trapping, using a laser source to hold the position of a microparticle in 3D, was developed over 30 years ago. However it cannot directly manipulate objects greater than a few microns, and has been extensively covered in the literature, though novel bioengineering uses are being developed.<sup>98</sup> If the particle is engineered asymmetrically, the beam does not have to be directional or focused, instead the thermophoretic effect propels the particle in a direction depending on the particle design and light wavelength.<sup>99</sup> Recently a mobile microrobot with a syringe function was developed by exploiting four optical traps manipulating four handles on the microrobot. In the center, they fabricated a metal layer that could generate bubbles and







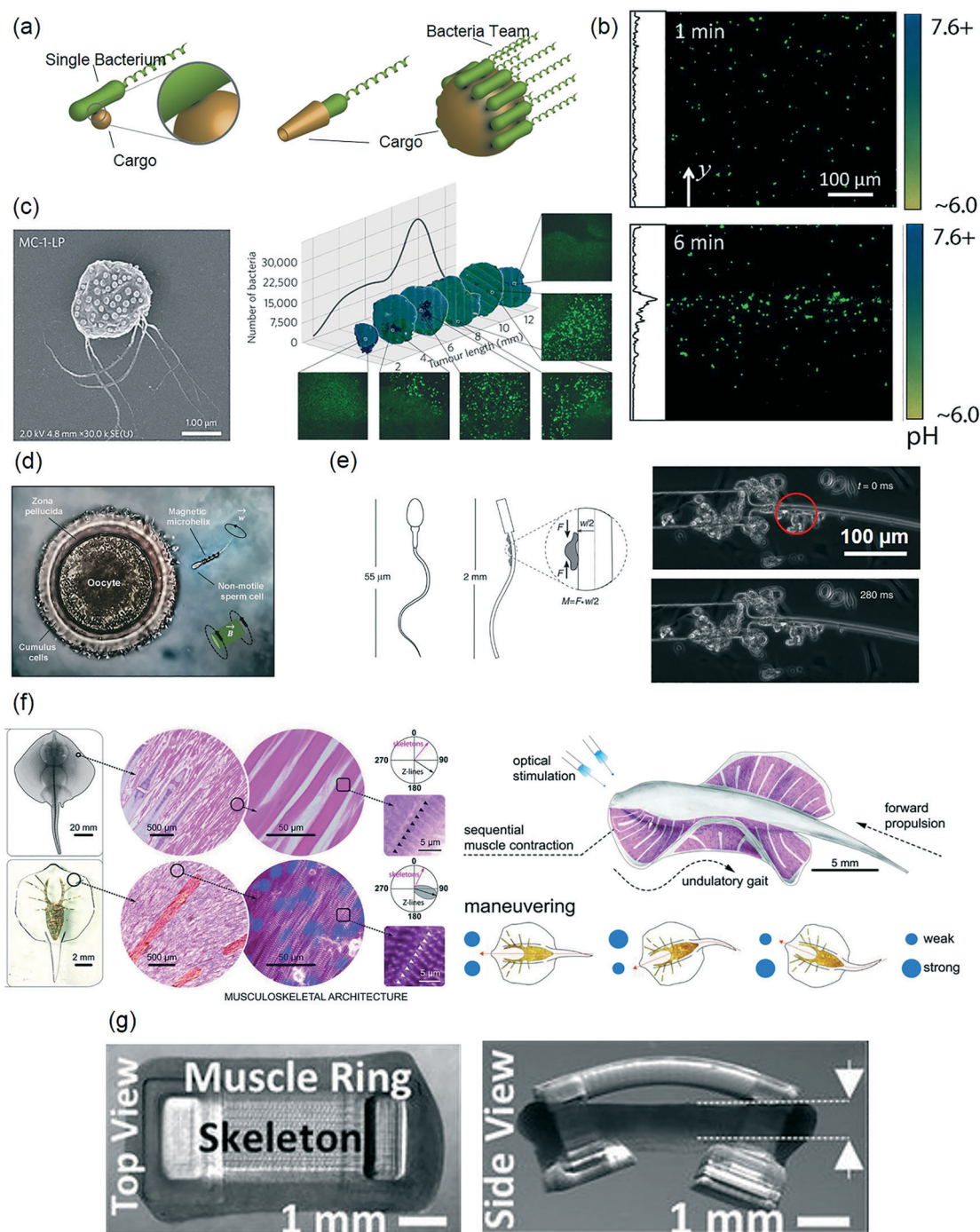


**Fig. 3** Chemically powered microrobots. (a) A schematic diagram of a bubble-propelled microswimmer motion step. The bubble makes a cyclic and asymmetric change from "bubble inside" into "detached bubble", which causes the motion of the microswimmer (reprinted with permission from ref. 114. Copyright 2011 from the Royal Society of Chemistry). (b) Speed modulation of hydrogen peroxide-based, bubble-propelled microswimmers by ultrasound. Application of the ultrasound disrupts the bubble evolution and hence reducing the swimming speed (reprinted with permission from ref. 115. Copyright 2014 from the American Society of Chemistry). (c) Maturation of effective bubbles for motion depends on the geometry of the film. The visible oxygen bubbles are formed only in the cavity of a tube. (I) Folding of stimuli-responsive films by cooling below 28  $^{\circ}C$ . (II) Unfolding by warming up with stopping of bubbles (reprinted with permission from ref. 116. Copyright 2014 from the John Wiley & Sons, Inc.). (d) Time-lapse images of zinc-based microrobots in gastric acid at 37  $^{\circ}C$  (1 s intervals, I-IV) (reprinted with permission from ref. 125. Copyright 2015 from the American Society of Chemistry). (e) Development of a rationally designed metabolic network for temporally sustained autonomous movement at constant speed (reprinted with permission from ref. 128. Copyright 2016 from the American Society of Chemistry). (f) Velocity control of a Janus micromotor by manipulating the enzymatic activity of urease (reprinted with permission from ref. 131. Copyright 2016 from the American Society of Chemistry). (g) Long-range directional motion of colloidal Janus particles, guided along prescribed topographic pathways (reprinted with permission from ref. 136. Copyright 2016 from Nature Publishing Group).





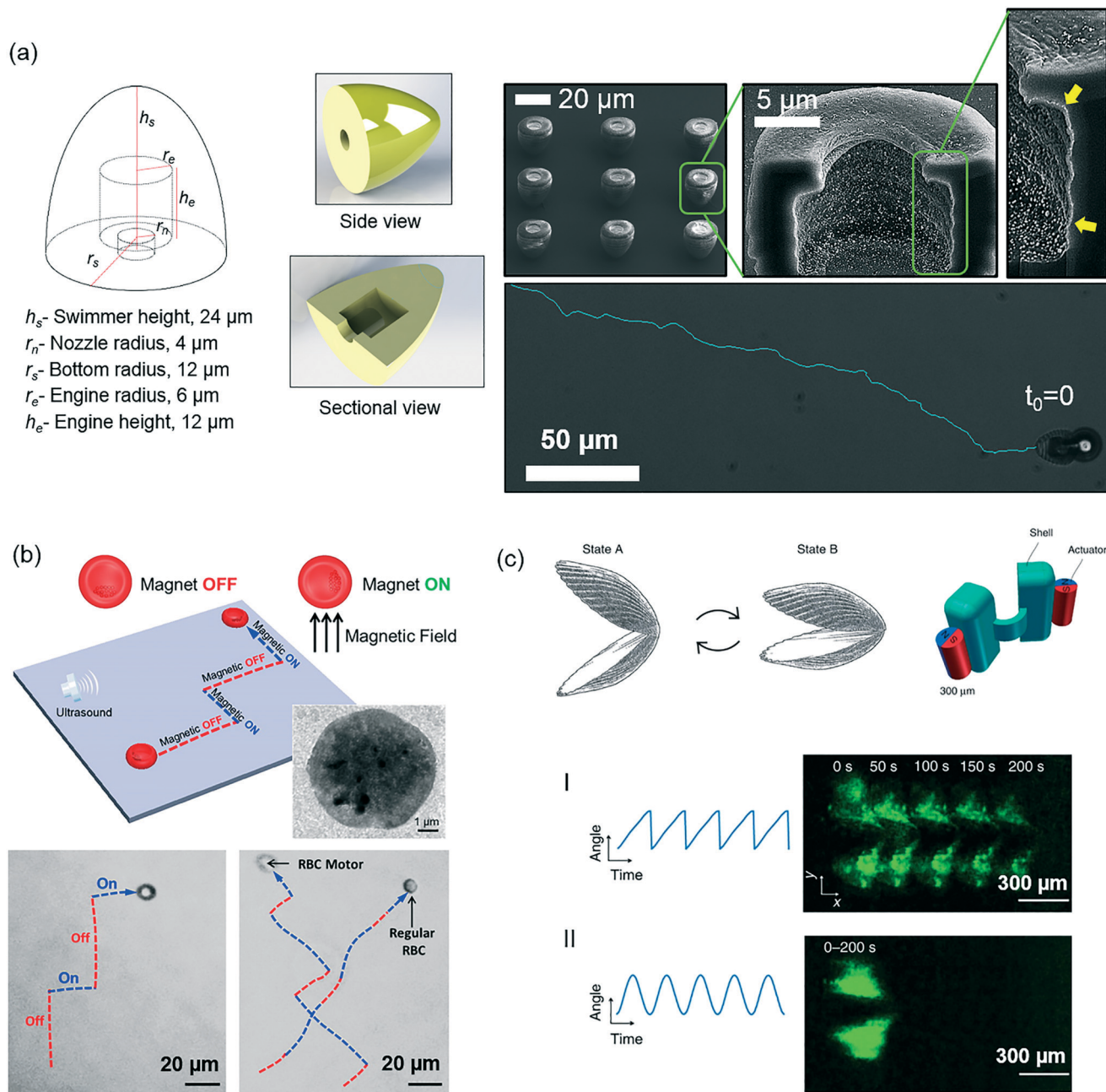




**Fig. 4** Biohybrid microrobot design and application strategies for bioengineering applications. (a) Conceptual designs of bacteriobots by attaching motile bacteria to synthetic drug cargos (reprinted with permission from ref. 137. Copyright 2016 from Elsevier). (b) Fluorescent micrographs of bacteriobots demonstrate pH-triggered accumulation over time, indicating a uniquely coupled motion and sensing capability of biohybrid designs (reprinted with permission from ref. 148. Copyright 2015 from Nature Publishing Group). (c) Left: Magneto- and aero-tactic bacteria *Magnetococcus marinus* strain used to make a nanoliposome-bacteria biohybrid construct to target mouse tumor. Right: Transverse tumor sections actively populated by the bacteria (reprinted with permission from ref. 152. Copyright 2016 from Nature Publishing Group). (d) An immotile sperm is captured by a remotely controlled magnetic helix and delivered to the oocyte for fertilization (reprinted with permission from ref. 1. Copyright 2016 from the American Chemical Society). (e) An elastic 1D filament with a rigid head and a compliant tail, and a small, single cluster of muscle cells generating power to create asymmetric motion for swimming (reprinted with permission from ref. 160. Copyright 2014 from Nature Publishing Group). (f) Musculoskeletal meso- and micro-architecture of a skate, *L. erinacea* is replicated in a 2D tissue-engineered ray. Upon optical stimulation, the tissue-engineered ray induces sequential muscle activation via serpentine-patterned muscle tissues, generates undulatory locomotion, and sustains steady forward swimming. It changes direction by generating asymmetric undulating motion between left and right fins, modulated by light pulse frequency (reprinted with permission from ref. 158. Copyright 2016 from the American Association for the Advancement of Science). (g) Optogenetic 3D muscle ring-powered biobots (reprinted with permission from ref. 157. Copyright 2016 from the National Academy of Sciences of the U.S.A.).







**Fig. 5** Some of the critical future considerations in microbotics concerning fabrication, materials, and design aspects. (a) CAD-designed and 3D-microprinted microrobots with patterned chemical regions can enable encoding complex microrobotic tasks and functions (reprinted with permission from ref. 166. Copyright 2017 from John Wiley & Sons, Inc.). (b) Red blood cells represent a rich source of making massive numbers of microrobots that are immunogenically safe and patient-specific for targeted cargo delivery applications (reprinted with permission from ref. 167. Copyright 2014 from the American Chemical Society). (c) Designing microrobot mobility components that are efficiently propelling in the complex viscoelastic physiological environment is central. The current designs that are typically optimized to operate in Newtonian fluids, e.g., water, may need revisiting for *in vitro* and *in vivo* scenarios, especially taking the particular body location and local properties of the physiological fluid into account (reprinted with permission from ref. 169. Copyright 2014 from Nature Publishing Group).

at a size scale that can non-invasively access to small spaces. For example, individual cells or cell packs organized in unit tissue scaffolds could be assembled by means of a off-board powered microrobot for obtaining 3D heterogeneous tissue-mimetic constructs.<sup>2</sup> Particularly, the assembly of 3D parts, which require orientation and positional control, would be best addressed using microrobotic assembly. Handling small

objects in very small fluid volumes for manipulation, moving and reconfiguring the components by means of 3D micro robots could make this route highly attractive for organ-on-a-chip applications where complex cellular materials with 3D microscale compositional features are positioned.

Fabrication of microrobots, in both on-board and off-board approaches, presents unique challenges concerning



design, fabrication process, and encoding operational capabilities. Conventional microfabrication techniques usually provide relatively simple geometric structures, such as tubes, spheres, and surfaces, with limited design flexibility and function. For example, a bubble-propelled micromotor requires well-compartmentalized placement of the catalyst and effective ejection of the jet bubbles in order to produce efficient propulsion from the catalytic reaction. On the other hand, realization of complex designs with programmable distribution of the catalyst and other functional components is a daunting task at the microscale. For this reason, the majority of the bubble-driven microswimmers are in the form of tubes, made with either electrodeposition or rolled up polymer films, and the catalyst is homogeneously present everywhere located in the innermost layer.<sup>165</sup> Besides, because the propulsion in the low Reynolds regime suffers greatly from the viscous drag, an optimal 3D microswimmer body design is an important parameter to achieve the maximum propulsion efficiencies.

Integration of computer-aided design (CAD) to microfabrication technologies has been a significant advancement to realize sophisticated 3D designs that could not be conceivable with the existing methods. To this end, application of additive manufacturing processes enabled by two-photon crosslinking, also known as direct laser writing technology, has opened up an unprecedented 3D design and manufacturing freedom at the microscale. In regard to its microrobotic applications, Servant *et al.* used this technology to develop cork-screw-type magnetic microswimmers.<sup>70</sup> Very recently, Ceylan *et al.* has advanced this technology by adding chemical versatility to the 3D-printed bodies, and thereby realizing the first computer-designed and low drag bubble-propelled microswimmers (Fig. 5a).<sup>166</sup> Tailorable local 3D chemical properties would allow advanced programmable functionalities, and hence could lead to novel design opportunities for microrobots.

Material biocompatibility is an important aspect for devices to operate in the living environment. This has attracted little attention so far, while accumulating knowledge and expertise in tissue engineering and related disciplines could provide a wealth of inspirations regarding type and composition of the materials for fabrication of microrobots. When a microrobot is inside biological fluids it is prone to attacks by the cells of immune system, and its circulation time is closely related with the time of recognition by the host immune system. A possible approach could be the use of patient's own biomaterials to fabricate the microrobot bodies. Such a personalized solution could largely circumvent the immune response, as the body would recognize the microrobots as self. For example, turning natural red blood cells into functional micromotors by loading them with magnetic nanoparticles is a promising example toward this purpose (Fig. 5b).<sup>167</sup> Wu *et al.* developed such systems, and could propel them by ultrasound and guide them by magnetic fields. These cells are vastly available in the blood, as such 2.4 million of those cells are being produced each second.<sup>168</sup> Use of red blood cells as

the base material could be interesting and useful to enable massive amounts of microrobots that could be hardly achieved by any of the existing microfabrication technologies. Moreover, they are mechanically robust and can change shape under applied stress without undergoing plastic deformation. They have an average of 120 days lifetime, during which they travel around 400 km.<sup>168</sup> Design systems based on red blood cells could therefore greatly help robust locomotion in blood vessels by dynamically adjusting their diameters.

In the earlier sections, we emphasized the importance of non-reciprocal motion in the low Reynolds numbers for a microswimmer to propel. However, most biological fluids are non-Newtonian, and thereby exhibiting viscoelastic behavior. This environment is vastly different from what the scallop theory was based upon, *i.e.*, Newtonian fluids. Qiu *et al.* realized that a microswimmer can also move with reciprocal periodic body-shape changes in non-Newtonian fluids (Fig. 5c).<sup>169</sup> The net propulsion here is caused by the modulation of the local fluid viscosity by varying the shear rate exerted by the swimmer body itself. This demonstration opens new design considerations for microrobots that are built to operate in non-Newtonian physiological fluids. Moreover, the existing microswimmers may need to be revisited for their optimal design and performance in the living environment, in which their propulsion speed, energy efficiency, and control may significantly vary.

## Glossary

Microrobot	A reprogrammable, microscopic machine with partly or fully self-contained capabilities entitled by on-board motion, perception, and learning.
Micromotor	A component of microrobot that can convert energy from various sources, such as magnetic fields, light, or chemical bonds, to do mechanical work in the form of directional motion.
Microswimmer	A specific locomotion mode of a microrobot that is able to propel and do directional motion in bulk fluid.
Off-board approach	Remotely actuated, powered, and steered microrobots.
On-board approach	A microrobot is self-contained with all the components necessary to move, sense, and operate in a manner independent from an external intervention.
Biohybrid design	Single-celled microorganisms are physically incorporated with synthetic materials to exploit cells' integrated powering, motility, and sensing capabilities.
Fuel	Chemical that is consumed by the micromotor to produce thrust force.





Functional component Components of a microrobot apart from its mobility, such as drug cargo, gripper, controlled release system, and sensing.

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