IEEE Open Journal of
Nanotechnology

Received 27 November 2020; revised 23 December 2020; accepted 5 January 2021. Date of publication 12 January 2021;
date of current version 5 February 2021. The review of this article was arranged by Editor Z. Nasiri-Gheidari.

Digital Object Identifier 10.1109/OJNANO.2021.3050496

Micromanipulation With Microrobots

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This work was supported in part by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health under Award Number R01EB016458. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ABSTRACT Microrobots are promising tools for applications that require micromanipulation, such as single-cell manipulation and surgery, tissue engineering, and desktop manufacturing. This paper briefly reviews common microrobot actuation mechanisms, then reviews current progress in several capabilities that are desirable for micromanipulation, with an emphasis on optothermal microrobots.

INDEX TERMS Microrobots, microrobotics, micromanipulation, microassembly.

I. INTRODUCTION

Micromanipulation is a capability that benefits many application areas, including the fabrication of electronic circuits and devices [1], single-cell analysis [2], drug delivery [3], pathogen isolation [4], minimally invasive surgery [5], and tissue engineering [6]. While there are many methods and technologies that are capable of manipulating microscale objects, this paper will focus on microrobots. Microrobots are robotic systems in which untethered mobile components have all dimensions between 1 μm and 1 mm, so that the mechanics are dominated by microscale forces. Microrobots offer a variety of manipulation methods, including contact and non-contact manipulation. Microrobots also generally feature robust, automated control systems, making it easier for operators of various skill levels to perform micromanipulation.

Several microrobotic actuation mechanisms suitable for micromanipulation will be described. Desirable features of micromanipulation using microrobots will be discussed, and recent progress in implementing these features will be discussed, with an emphasis on optothermal microrobots.

II. MICROROBOT ACTUATION MECHANISM

Microrobotic actuation spans a variety of methods, including magnetic actuation, electrostatic actuation, biohybrid systems, optothermal actuation, acoustic actuation, and combinations of these approaches. These actuation mechanisms will be briefly discussed in this section. Some characteristics of each type of actuation are summarized in Table 1.

TABLE 1. Actuation Mechanisms for Microrobots

Actuation mechanism	*Achievable velocity*	*Resolution*	*Multiple microrobots**
Magnetic	~ 300 mm/s [53]	~ µm [77]	Up to 3 [54], [100]
Electric	~ 35 mm/s [21]	~ 3 µm [22]	Up to 5 [22]
Biohybrid	~ 0.8 mm/s [24]	~ µm [25]	Not yet [26], [29]
Optothermal	~ 1 mm/s [33]	~ µm [64]	Up to 50 [38]
Acoustic	~ 7.5 mm/s [44]	~ µm [41]	Not yet [101]
Multiple forces	~ 8 mm/s [49]	~ 0.05 µm [102]	Up to 2 [49]

*This category refers to the number of microrobots that can be simultaneously moved along unique and non-parallel trajectories.

A. MAGNETIC FORCES

A popular approach to the actuation of microrobots is the use of magnetic force and torque [6]–[10]. Magnetic forces can be relatively large (nN to N) [11], [12], and magnetic fields can penetrate human tissues with minimal side effects. Thus, many microrobot systems being developed for *in vivo* applications such as drug delivery or targeted therapeutics use magnetic fields. Magnetic actuation is also amenable to integration with other systems, such as imaging systems: magnetic resonance imagers can be used to actuate magnetic microrobots [8], [13]. The magnetic fields can also act upon many magnetic microrobots at once [14], [15]. Drawbacks to magnetic actuation include difficulties in creating highly localized magnetic fields, and the high current requirements of electromagnets. Also, the independent actuation of many magnetic microrobots is challenging due to identical control inputs. Progress on this topic has been achieved through several approaches: 1) spatially and temporally varying the magnetic force on the microrobots [14], [16], 2) using heterogeneous microrobots which are geometrically and/or magnetically distinct, creating individualized responses to the applied magnetic fields [17]–[19] and 3) taking advantage of inhomogeneities in the magnetic field and/or field gradient [15], [20].

B. ELECTRICAL FORCES

Electrical forces are also popular for microscale actuators, and have been employed for microrobot actuation [1], [21]–[23] Electric fields easily localized, helping to increase the actuation resolution. The equipment and setup for electrical actuation is also usually simpler and more compact compared to other actuation methods. However, high electric fields may have harmful effects on some types of microscale objects, such as living cells. Electrical actuation in electrically conductive fluids can also be challenging, due to joule heating and undesirable electrically conductive pathways. Thus, electrical actuation is better suited for micromanipulation of non-biological samples.

C. BIOHYBRID SYSTEMS

Naturally occurring organisms such as motile cells and bacteria are capable of microscale locomotion, along with other capabilities, such as moving along chemical gradients. Thus, there has been efforts to harness these organisms to actuate microrobots [24]–[31]. Biohybrid microrobots integrate living organisms with an artificial structure. The materials or surface chemistry of the artificial structure can also be modified for advanced functionalities such as drug transport [30] and targeted cellular interactions [31]. This is a promising area of work, but living cells are subject to additional constraints on their working environment. Biohybrid systems could be used for applications *in vivo*, but they must be designed so that there are no adverse effects to the body.

D. OPTOTHERMAL FORCES

Optothermal forces are thermal forces that are caused or controlled by an optical source [32]. Thermal forces that can be generated include surface tension gradients [33] and thermal Marangoni convective flows [34], [35], as well as thermophoresis, which can move particles subjected to a thermal gradient [36]. The temperature gradients necessary to generate these thermal forces can also be created using resistive heaters or other heating elements [37]. However, using an optical source does confer an advantage: it is straightforward to focus light into microscale patterns, so high-resolution actuation forces can be created without any microfabrication. Optothermal forces can be gentler on payloads as compared to optical manipulation that directly converts the photon momentum into mechanical force, as the objects under manipulation do not have to be directly illuminated by the light [32], [33], [38]. However, it is usually more complicated to set up optical equipment compared to the equipment needed for the other actuation methods, and optical setups are also usually expensive. Optothermal actuation is better suited for *in vivo* applications, although it is possible to efficiently transmit light into the body using minimally invasive fiber optic probes.

E. ACOUSTIC FORCE

Acoustic forces, including acoustic radiation or acoustic streaming, can be used for microrobot actuation. A standing acoustic wave produces acoustic radiation that drives micro-objects to the acoustic pressure nodes and anti-nodes. Acoustic radiation has been used to actuate synthetic microrobots [39]–[42] and acoustic streaming has been used for bubble oscillatory propulsion of microrobots [43]–[45]. Acoustic fields are able to propagate inside human body, which is a desirable feature for microrobotic actuation. Acoustic actuation is relatively strong and can propel microrobots at up to 7.5 mm/s [44] in biofluids, even those with high viscosity and high ionic strength [46]. However, it is challenging to control microrobots individually, and creating acoustic standing waves can complicate *in vivo* applications. Nevertheless, acoustic forces are attractive for *in vivo* applications due to the ease of transmitting these waves through tissues.

F. MULTIPLE FORCES

Combinations of the aforementioned actuation mechanisms are also used, which helps to address shortcomings of or add functionality to a particular actuation method. For example, biohybrid systems often need an additional applied field to steer the bacteria- or cell-powered microrobots, such as a magnetic field [4], an electrical field [47], or an optical field [48]. Other combinations of actuation mechanisms have also been explored, such as magnetic actuation with an electrostatic anchoring force [49], magnetic actuation with light stimulated drug release [50], optothermal bubble generation with acoustic-driven fluid streaming [51], and acoustically actuated magnetic field controlled microrobots [52].

III. MICROMANIPULATION WITH MICROROBOTS

Micromanipulation with microrobots benefit from the capabilities that are highlighted in this section. The recent progress in each of the capabilities is discussed, with an emphasis on work done using optothermal microrobots.

A. INCREASING THROUGHPUT OF MICROMANIPULATION

Micromanipulation can be completed more rapidly at a higher throughput, referring to the number of micromanipulation operations per unit time. A straightforward method to increasing the throughput of micromanipulation operations is to increase the actuation velocity of the microrobots. Microrobots have been actuated at up to tens of cm per second [53], but this means that the speed of the control system and the microrobot position-sensing system (usually an optical microscope with a camera) also needs to be sufficient to accurately move the microrobot.

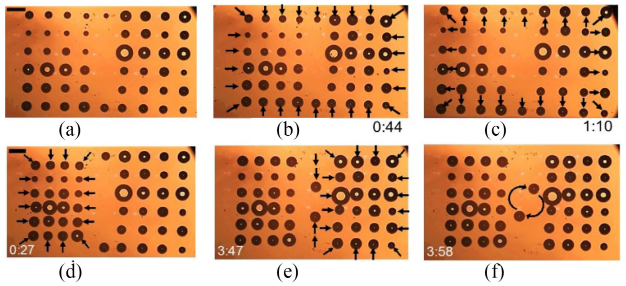

FIGURE 1. **Independent actuation of fifty OFB microrobots in parallel [38]. (a) Fifty OFB microrobots were serially generated by optothermal heating. Each OFB microrobot is controlled by a point of an optical pattern projected onto the workspace. (b, c) Parallel actuation of fifty microrobots independently, each in a different direction. (d–f) A team of 24 and a team of two microrobots were actuated in linear and circular trajectories. Scale bars: 150 μm.**

The throughput of micromanipulation using microrobots can also be increased by using multiple microrobots. Magnetic and electrical actuation are capable of moving multiple microrobots in parallel [15], [22], [23], [54], [55], but if global actuation signals are used, microrobot trajectories are usually coupled to one another. To decouple the movements of multiple microrobots, specialized working surfaces can be used to create localized forces that force the microrobots to travel along different trajectories [23], [33]. Alternatively, each microrobot can be designed to have an individualized response to a global actuation signal, such as by varying the dimensions of the actuation structures [15], [22], [54], [56], [57].

Biohybrid microrobots such as bacteria-propelled microrobots can have motion that is uncoupled from one another [25], [58]. This makes this approach promising for multiple microrobot micromanipulation [26]. However, to fully realize this promise, more work needs to the done on the positioning accuracy and repeatability of biohybrid microrobots.

Optothermal actuation allows the parallel actuation of many microrobots, as demonstrated by opto-thermocapillary flow-addressed bubble (OFB) microrobots. The OFB microrobots are gas bubbles in a liquid that move along optically generated thermal gradients [33], [59], [60]. As the OFB microrobots are optically addressed, the uncoupled actuation of individual microrobots can be achieved, even when moving many microrobots at once.

The independent actuation of 50 OFB microrobots in parallel was previously demonstrated (Fig. 1) [38]. The microrobots could simultaneously move in different directions, showing uncoupled parallel actuation. This independent actuation of multiple microrobots enabled cooperative micromanipulation, reducing the time necessary to transport multiple micro-objects [38].

Microrobot actuation parameters such as speed, resolution, and throughput can be improved by using functionalized substrates and microfluidic devices. For example, for optothermal microrobots actuated in saline solution inside an open reservoir, coating the substrate with a hydrophilic PEG layer [61], [62] reduced drag and increased the actuation speed by 16 times. Higher-throughput optothermal microrobot actuation was also demonstrated using Ti-coated substrate compared to α-Si- coated substrate [38]. Another example of a specialized substrate enabled the actuation of multiple magnetic microrobots; selected robots were magnetically driven while other selectively fixed using an array of interdigitated electrodes on the substrate that provided electrostatic anchoring [49]. Moreover, on-chip actuation in microfluidic devices allows 3D maneuverability and high-resolution micromanipulation [63]. The combination of microfluidics and high-speed (~280 mm/s) magnetic microrobots enabled high-throughput micromanipulation [53].

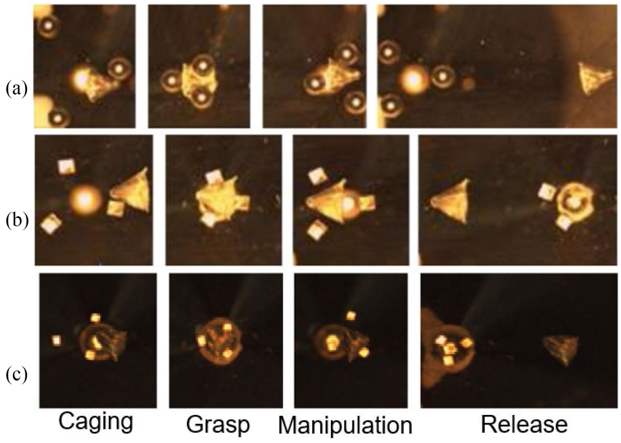

FIGURE 2. **Cooperative micromanipulation by grasping using magnetic microrobots. (a–c) Micromanipulation using spherical, 500-μm, and 250-μm cubical microrobots. Reproduced with permission [15]. Copyright 2015, IEEE.**

B. INCREASING RESOLUTION OF MICROMANIPULATION

Micromanipulation with microscale precision (or better) is important for applications such as tissue engineering. Precise positioning of a payload can be achieved by employing grasping or caging [15], [38]. Caging refers to positioning multiple microrobots surrounding an object so that neighboring microrobots are placed at a distance smaller than the size of the micro-object (Fig. 2 & 3). Grasping refers to multiple microrobots in contact with a micro-object (Fig. 2). OFB microrobots have demonstrated micromanipulation with increased resolution with caging and grasping [64]. As an example, a spherical OFB microrobot has difficulty pushing or pulling a spherical micro-object on a linear trajectory [62]. However, multiple OFB microrobots were able to grasp spherical and planar micro-objects with increased spatial and temporal resolution [38], [64].

Magnetic microrobots actuating under global magnetic forces demonstrated cooperative micromanipulation by grasping [15]. A focused conical-shaped magnet was used to actuate magnetic microrobots in a cooperative manner for micromanipulation. Two different shapes of microrobots were able to stably manipulate similar micro-object with high resolution by caging and grasping [15].

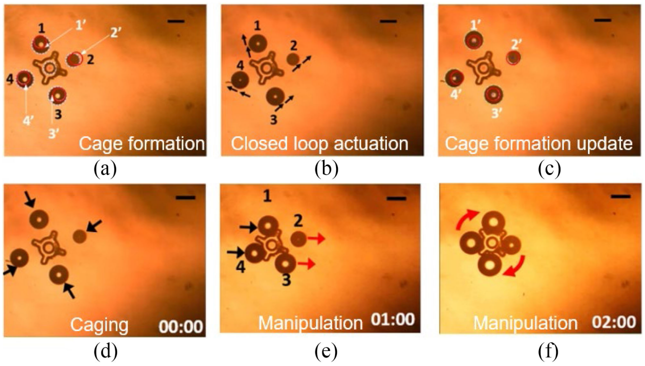

FIGURE 3. **Caging, grasping, and manipulation of a planar micro-object [64]. (a–c) Stable caging of a micro-object through closed-loop control and path planning. The microrobots are labeled 1 to 4; the positions for the microrobots to form the cage are labeled 1′ to 4′. (d-e) Grasping a micro-object that is adhered to the surface. (f) Rotating the micro-object frees it from the surface for further manipulation. Scale bars: 150 μm.**

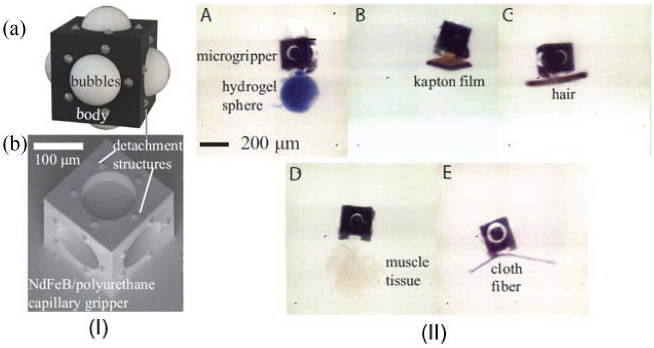

FIGURE 4. **An untethered magnetic capillary microgripper. (I) The capillary microgripper is cube-shaped with bubbles on five sides (a). (b) SEM image of the fabricated capillary microgripper. (II) The capillary microgripper was used to capture and transport various micro-objects including a (A) hydrogel spheroid, (B) 25-μm-thick Kapton film, (C) human hair, (D) muscle tissue, and (E) cloth fiber [68]. Reproduced with permission. Copyright 2016, Royal Society of Chemistry.**

C. INCREASING DIMENSIONALITY OF MICROMANIPULATION

Micromanipulation is commonly performed in two dimensions, but adding control in the third dimension helps with a wide range of applications in biomedical and tissue engineering, such as the construction of artificial tissues by arranging microscale hydrogels laden with cells (microgels) [65], [66]. One way to achieve 3D manipulation is by using a crawling magnetic microrobot to assemble a layer of micro-objects, then using a microfabricated ramp to elevate the microrobot for the assembly of the next layer [67]. A maximum of three layers of microassembled objects have been demonstrated using this method. Alternatively, an untethered magnetic microgripper demonstrated multi-layer assembly of microgels up to ten layers [65]. The microgripper could open and close its jaw to grab micro-objects, and is capable of assembling more layers in the z-direction compared to manipulation by pushing [67].

Pick-and-place manipulation of micro-objects was also demonstrated by an untethered magnetic capillary microgripper [68]. The body of the magnetic microrobot contains a cavity that hosts an air bubble, which provides capillary forces to pick up micro-objects. The bubble can be retracted to reduce the contact radius, releasing the micro-object [68] (Fig. 4).

The microrobot itself can also act as a microcarriers in three dimensions, transporting nano-components adhered to it. Large numbers of magnetotactic bacterium carrying liposomes were actuated to a target location using magnetic force in a fluidic 3D environment [69]. 3D actuation of various microrobots uses different control strategies based on the actuation mechanisms. As an example, a type of magnetic microrobot uses a tri-axial Helmholtz coil system that has six independent coils [9], whereas optical microrobots are controlled by varying the light frequency, polarization, exposure time, pulse duration, and focal plane [70]–[73].

D. INCREASING ROBUSTNESS OF CONTROL SYSTEMS

The functionality of the various types of microrobots is highly dependent upon a robust control system. Multiple microrobot systems or microrobots that be actuated quickly are challenging for humans to operate, so a capable control system is important. For example, the actuation of multiple OFB microrobots was first demonstrated in 2012 [74], but it was constrained by manual control by a single operator. This is made more complicated since OFB microrobots have a risk of merging when in contact with each other. The OFB microrobot system was made more robust by using a closed-loop control system capable of actuating each microrobot with knowledge of the location of other microrobots and micro-objects within the workspace [64]. Vision-assisted image-feedback control allowed path planning, grasp planning (Fig. 5), collision avoidance, and cooperative micromanipulation using multiple microrobots [64]. The closed-loop control increased the accuracy of the microrobot placement by 50% compared to one iteration of open-loop actuation [64].

Robust control systems were implemented with other types of microrobots, as well. A vision-based feedback-control system with real-time object detection was used for adaptive path planning around dynamically changing obstacles for chemically powered microrobots [75]. Closed-loop control allows high speed actuation of microrobots with high resolution. A magnetic microrobot was actuated up to 6 mm/s with position accuracy of 6 μm or better using vision-based closed-loop control (Fig. 6) [76]. Closed-loop control also improves the actuation accuracy in challenging situations such as 3D actuation in a viscous fluid [77].

An alternative to increasing the functionality and complexity of the control system is to imbue the microrobots themselves with more intelligence and autonomy in their movement. This can take several forms, including microrobots that autonomously move in response to environmental stimuli [78], [79]. Microrobot swarms are another approach. Similar

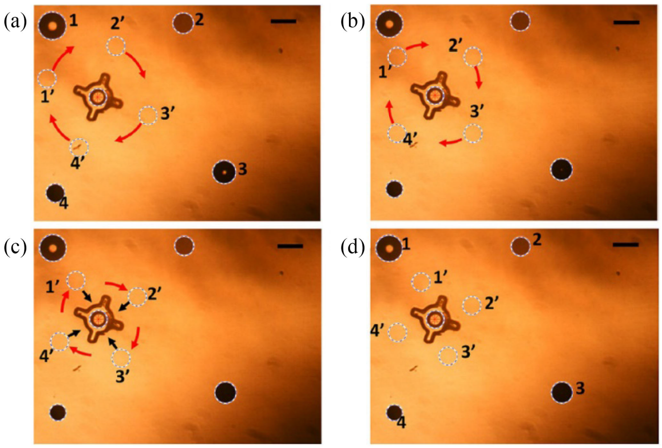

FIGURE 5. **Closed-loop control and path planning for the stable caging and grasping of a planar micro-object [64]. (a–c) Video from the microscope camera is analyzed to calculate the optimum locations (numbered 1′ to 4′) for caging the micro-object based on the current location of four (numbered 1 to 4) microrobots and the orientation of the micro-object. (a) The initial caging locations are shown, created by finding points equidistant from the center of the micro-object. (b) and (c) The optimal caging locations are shown, based on the orientation of the star-shaped micro-object. (d) Initial and target location of the microrobots for caging. Scale bars: 150 μm.**

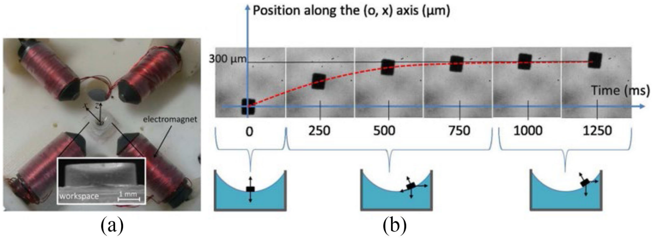

FIGURE 6. **High-speed closed-loop magnetic microrobot control. (a) Setup for magnetic actuation. The inset shows the 4-mm diameter cylindrical workspace, which is a liquid reservoir. The microrobot is placed and actuated at the air-liquid interface. (b) When the magnetic coils are energized, the microrobot is actuated at the meniscus. A camera is used to detect the microrobot position for the closed-loop control system [76]. Reproduced with permission. Copyright 2017, IEEE.**

to swarms of animals in nature, microrobots can move cooperatively by following a few simple rules, which can help with micromanipulation tasks [80]–[85].

E. ADDITIONAL MICROMANIPULATION CAPABILITIES

In addition to the transport, trapping, and assembly of micro-objects, additional micromanipulation capabilities can be realized using microrobots. This can be accomplished by adding end-effectors or structures to the microrobots for specific purposes, such as cutting into cells [86], performing biopsies [87], or measuring forces [88].

Another useful function is the ability to lyse specific single cells on demand, for further genetic or proteomic analysis. This function has been demonstrated in the same system used for OFB microrobots [89]. Microsecond laser pulses were used to generate vapor microbubbles that rapidly and repeatedly expanded and collapsed, creating microstreaming that is strong enough to lyse a cell positioned above the microbubble. This functionality can be combined with the microassembly capabilities of the OFB microrobots (Fig. 7) [89].

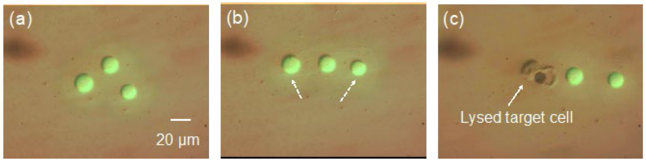

FIGURE 7. **Manipulation and lysis of cells using the OFB microrobot system [89]. All photos are composites of bright-field and fluorescent microscope images. (a) Initial position of three cells, labeled with a green Calcien AM dye. (b) The cells after assembling them into a horizontal line. (c) A single targeted cell was lysed, without affecting the neighboring cells.**

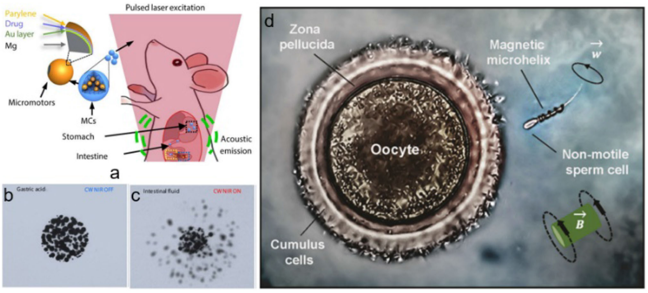

FIGURE 8. **Microrobots for the delivery of therapeutics. (a) Schematic of a photoacoustic microrobot for drug delivery in the gastrointestinal system of living mice. (b) Without NIR irradiation, the drug capsules remain intact in gastric acid. (c) Irradiation triggers release of the drug. Reproduced with permission from ref. [94] © AAAS. (d) A helical magnetic microrobot delivers an immotile sperm cell to an oocyte for fertilization [92]. Reproduced with permission. Copyright 2015, American Chemical Society.**

By making the lysis process more gentle, temporary disruption of the cell membrane can also be induced [90]. If this is done carefully, the cells survive, making this a useful technique to deliver payloads to specific single cells. This poration method can maintain high poration efficiency and cell viability (both at 95.1 ± 3.0%) [90].

Microrobots can also be used to deliver localized therapeutics *in vitro* and *in vivo*. Potential payloads include drugs, cells, genetic materials, and nanoparticles. Among the various types of microrobots bacterial biohybrid microrobots are popular due to their performance in bio-microenvironments [30]. For example, a biohybrid algal microrobot coated with chitosan nanoparticles was used to deliver chemotherapeutic cargo to SK-BR-3 cancer cells *in vitro* [91]. In a different *in vitro* application, a magnetic microhelix demonstrated the capture, transport, and release of functional but immotile sperm to an oocyte inside a microfluidic channel (Fig. 8(d)) [92]. An example of *in vivo* drug delivery is the use of a biohybrid microrobot to deliver bioluminescent genes to various organs in mice [93]. Capsule microrobots were also used for *in vivo* drug delivery, in mice intestines. After being administered orally into the mouse, the microrobot capsule was monitored in real time using photoacoustic computed tomography, and near-infrared light was used to control the propulsion of capsule as well as serving as a trigger for the release of cargo at the targeted location (Fig. 8(a)–(c)) [94].

Microrobots were also used for the study of cell and tissue mechanics in the field of mechanotransduction [95] and mechanobiology [96]. The untethered nature of microrobots is important for mechanobiology applications such as microforce sensing [97]. A 2D elastic end-effector mounted on a magnetic microrobot can measure the force applied on a bio-object within a range of 0 to 20 μN with a resolution of 1.5 μN [88] using a vision-based technique.

IV. OUTLOOK

Microrobots are promising because of their small size, wireless mobility, and their ability to navigate in small, confined, and hard-to-reach sites. The recent progress in medical and bio-microrobots shows promise in near future applications in minimally invasive interventions and targeted diagnosis and therapy. After significant improvement on design, fabrication, actuation, and control methods of microrobots, the focus is shifting to using and adapting microrobots for particular applications and tasks. It is anticipated that the *in vitro* and *in vivo* biomedical applications of microrobots will be prioritized [6], [29], [30], [65], [98], [99]. *In vitro* applications such as cell assembly, cell lysis, and drug delivery require high throughput, and robust control mechanisms. Therefore, optical and bio-inspired microrobots are most likely to be the focus in near future for *in vitro* applications. On the other hand, *in vivo* applications such as targeted drug delivery, microrobot-aided surgery, and micro-biopsy are also being actively investigated for clinical use. Hence, actuation signals which can penetrate tissues, such as magnetic fields and ultrasonic waves are more likely to be employed for *in vivo* translational clinical applications.

V. CONCLUSION

Microrobots are useful tools for micromanipulation, and further development can make them more robust, with increased functionality. To date, microrobots have proven useful for relatively specialized applications such as minimally invasive surgery [5] and drug delivery [30], [92]–[94], but applied use of microrobotic systems remains at an early stage. Increasing the robustness and user-friendliness of microrobotic systems can help with increased adoption. Areas to be developed towards this goal were described in Section III, and include increasing micromanipulation throughput, increasing micromanipulation resolution, adding more degrees of freedom of the micromanipulation, improving upon control systems, and adding capabilities beyond micro-object trapping, transportation, and assembly. In addition, as more medical applications are explored, application-specific functionalities will need to be realized.

ACKNOWLEDGMENT

The authors thank their collaborators that made this work possible: Dr. Wenqi Hu, Kelly Ishii (early OFB microrobot work), Dr. Qihui Fan (cell surgery work), Julian Cheng, Prof. Zhidong Wang, Dr. Noboru Takahashi, Nigel Ng, Kawai Siliga (OFB microrobot control system work).

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