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Publication Date:
2017-12

Permanent Link:
https://doi.org/10.3929/ethz-b-000192698 →

Originally published in:
Applied Materials Today 9, http://doi.org/10.1016/j.apmt.2017.04.006 →

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Recent developments in magnetically driven micro- and nanorobots

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Abstract

Micro- and nanorobots are promising devices for biomedical and environmental applications. The past few years have witnessed rapid developments in this field. This short review intends to address recent progress on magnetically driven micro- and nanorobots developed in our laboratory and by other research groups. Different designs such as helical swimmers, flexible swimmers, surface walkers, and others are categorized and discussed. Specific applications of these robots in the fields of biomedicine or environmental remediation are also reported. Finally, the use of magnetic fields for additional capabilities beyond manipulation is presented.

Keywords:

Magnetic, microrobots, nanorobots, functionalization, magnetic hyperthermia, magnetoelectric

1. Introduction

Micro- and nanorobots are promising devices for applications in drug delivery, sensing, environmental remediation, and manipulation of small objects [1-11]. These machines convert energy into motion by scavenging fuel from their surrounding media [12-18], or by harnessing power from external energy sources such as light, ultrasound, electrical or magnetic fields, or combinations of these [19-25]. The use of magnetic fields for actuation is the most versatile option as this approach enables a wide variety of swimming mechanisms and can simultaneously be exploited for additional functionalities. Furthermore, magnetically powered micro- and nanorobots are among the most promising miniaturized engines for biomedical applications because they do not adversely interact with tissues in a wide range of conditions.

The number of research efforts devoted to magnetic small-scale robots (MSSRs) has skyrocketed during the past decade due to advances in micro- and nanofabrication, and manipulation systems. This short review is intended to address the most recent progress on MSSRs developed in our laboratory and by other research groups. The review is focused on devices made of ferromagnetic and superparamagnetic materials. For more comprehensive reviews on the fundamentals of magnetic propulsion and the manipulation of other types of magnetic materials (i.e.: diamagnetic, paramagnetic) the reader is referred to previous publications [26-28]. Some specific applications of MSSRs in the fields of biomedicine or environmental remediation are also reported. Finally, the use of magnetic fields for additional capabilities such as hyperthermia [29], catalysis [30], and magnetoelectricity [31, 32] is presented.

2. Recent magnetic swimmer designs

2.1. Helical swimmers

Helical micro- and nanorobots can be propelled by rotating magnetic fields. Rotation of these machines around their helical axis generates a translational corkscrew-like movement. This locomotion strategy is widely adopted by several microorganisms such as bacteria, which rotate their flagella to swim at low Reynolds number regimes. Helical structures have been manufactured by several methods such as self-scrolling [20], direct laser writing (DLW) [33, 34], glancing angle deposition (GLAD) [35-40], template-assisted electrodeposition (TAE) [41], and biotemplating synthesis (BTS) [42].

Nelson's group, which pioneered the work on artificial bacterial flagella (ABFs) in 2007 [20, 43], has recently established several procedures for the fabrication of advanced helical micro- and nanoswimmers for several applications. Capitalizing on DLW, several helical ABF designs have been created. For instance, helical swimmers were directly printed using DLW and were rendered magnetic and biocompatible by means of physical vapor deposition (PVD) of Ni and Ti, respectively (Figure 1 a,b) [33, 44]. In the following, we refer to this method as DLW-PVD. This relatively simple high-throughput fabrication procedure has led to several interesting devices. For instance, the swimmers were functionalized with calcein-loaded liposomes for *in-vitro* targeted drug delivery to single cells [45]. The same helical platforms were later functionalized with lipoplexes containing plasmid DNA [4]. In this case, targeted single-cell gene transfection to human embryonic kidney cells was successfully demonstrated (Figure 1 c). Schmidt and co-workers also adopted this fabrication approach to produce helical structures to capture, transport and release sperm cells to the oocyte cell wall (Figure 1 d) [46]. Recently, Nelson, Kostarelos, and co-workers realized a major breakthrough in the use of these helical swimmers for biomedical applications [47]. For the first time, a magnetically driven swarm of ABFs were tracked *in vivo* in the peritoneal cavity of a mouse. These swimmers were functionalized with near-infrared contrast agents (NIR-797), which enabled the tracking of the swarm by means of optical fluorescence imaging.

All the above-mentioned helical swimmers contain a Ni film as a magnetic building block. In order to create highly biocompatible helical bodies, Nelson's group modified the DLW-PVD fabrication strategy using the biocompatible photoresist, ORMOCOMP®, which was subsequently coated with Fe for magnetic propulsion [44]. The Fe-coated ORMOCOMP®-based helices did not show cytotoxicity, and, in fact, cell viability of C2C12 mouse myoblasts was enhanced after 72 hours of incubation with the swimmers.

Optimization of several helical designs by DLW-PVD was also conducted in Nelson's group. For example, Tottori and Nelson reported the fabrication of artificial helical microswimmers with mastigoneme-inspired appendages (Figure 2 a) [48]. The speed of these swimmers could be tailored by modifying the ratio between the length and the interval of the appendages. In another effort, helical designs with single-threaded screw-shaped tails and tubular heads were developed to generate mobile fluidic traps in 3D for the transport of small objects such as microbeads (Figure 2 b, c) [49]. Later, Sakar and co-workers reported on helical microcarriers with ring-shaped structures on both ends of the carrier, which were used to demonstrate cooperative manipulation and transport of microbars [50]. Perhaps, one of the most complex designs fabricated using DLW-PVD was the compound microtransporter with a wirelessly controlled Archimedes screw pumping mechanism (Figure 2 d-j) [51]. These highly sophisticated microdevices consisted of a magnetically actuated screw with integrated parts encapsulated in a hollow cylinder. The entire device was manufactured without further assembly steps using DLW-PVD. The microtransporters were able to transport microparticles and nanohelices within microfluidic channels. Hwang and co-workers have also produced multimodal helical microswimmers with conical heads by means of DLW-PVD [52]. These devices can switch between different propulsion mechanisms, rolling, spintop motion and corkscrew swimming, by simply adjusting the direction and the frequency of the rotating magnetic field.

In collaboration with Nelson's group, Peters, Hierold and co-workers showed that DLW can be used to create superparamagnetic composite twist-type actuators with programmed magnetic anisotropy (Figure 3 a-d) [7]. An pioneering effort in this direction can be found in the publication of Kim et al. [53]. Their composite helical structures were printed using a dispersion of superparamagnetic magnetite nanoparticles in SU-8 negative photoresist. The particles were aligned during soft baking by applying a homogeneous magnetic field of 30 mT. The perpendicular alignment of particles with respect to the long axis of the helical body defined the easy magnetization axis in this direction, and, in turn, enabled these devices to perform corkscrew motion when subjected to rotating magnetic fields. Additionally, immobilization of human immunoglobuline on SU-8-based microswimmers was achieved by glycine grafting and subsequent treatment with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide:N-hydroxysuccinimide. By readapting the fabrication procedure of DLW of superparamagnetic composites, Peters et al. developed the successful fabrication of fully degradable superparamagnetic helical swimmers consisting of a poly(ethylene glycol) diacrylate - pentaerythritol triacrylate matrix (Figure 3 e) [54].

GLAD has been also employed for manufacturing helical swimmers. Fischer and co-workers reported one of the smallest magnetically actuated nanoscrews with filament diameters of approximately 70 nm [36, 38]. The swimmers were manufactured using a shadow-growth technique on patterned substrates by block copolymer micellar nanolithography. In comparison to larger helical swimmers, the nanopropellers were able to translate in hyaluronic acid solutions and exhibited enhanced propulsion compared to their swimming performance in other purely viscous fluids. GLAD was also used by Fischer et al. to produce magnetic micropropellers functionalized with urease, enabling the swimmers to move through gastric mucin gels [37].

TAE is also a widely adopted method to produce helical micro- and nanopropellers. DLW can also be used to create complex templates. Pané, Nelson and co-workers developed a process to write three-dimensional templates using positive-tone AZ9260 photoresist [41]. By sequential electrodeposition of CoNi alloy and polypyrrole within the template, hybrid artificial bacterial flagella were successfully fabricated. This process was further exploited to create 3D hybrid microstructures (pillars and helices) consisting of a magnetic CoNi head for wireless magnetic control, coupled to a photocatalytic heterojunction made of a bismuth oxide/bismuth oxychloride segment [11]. These water-cleaning agents were able to degrade rhodamine B dye with 90% efficiency in 6 hours.

Anodic aluminum oxide (AAO) and polycarbonate (PC) templates have been shown to be suitable patterns to electrochemically grow nanohelices. Pioneered by Park and co-workers, palladium nanosprings can be formed by electrodeposition of palladium-copper nanowires and subsequent selective etching of copper [55]. Wang and co-workers adopted this method to produce magnetically driven helical nanoswimmers with different dimensions [56]. With the appropriate pore template dimensions, nanohelices with varied diameter, length and pitch could be obtained. A magnetic layer of Ni was deposited on the surface of the nanosprings by electron beam evaporation. The same fabrication procedure was later employed by Wang's group to produce a magneto–acoustic hybrid nanomotor (Figure 3 f) [57], consisting of a magnetic helical structure and a concave nanorod end, which could be actuated with either magnetic or acoustic fields, or in the presence of both. The collective behavior of these nanomotors could be tailored using both acoustic and magnetic forces. Recently, Pané and co-workers exploited TAE for the production of helical swimmers [58]. Magnetically driven Ag-coated nanocoils were synthesized for efficient bacterial contact killing. The bactericide agents were highly effective against Gram-positive and Gram-negative bacteria strains. The locomotion capabilities of the Ag helices along with their antibacterial attributes make these swimmers ideal nanoplatforms to fight multidrug-resistant bacteria.

Helical micro- and nanorobots have also been produced by biotemplating synthesis. One of the first examples is the cobalt-based helical swimmer developed by Schuerle et al. [42]. The structures were obtained by coating self-assembled phospholipidic helices using electroless deposition of a magnetic multialloy. Later, inspired by the work of Yamada and co-workers [59], Wang's group reported the use of the helical xylem vasculature of plants to produce magnetic helical swimmers [60]. The spiral vessels were extracted by carefully stretching the leaves near the stem, followed by coating them with evaporated magnetic Ni and biocompatible Ti layers.

More recent work by Zhang and co-workers reported the manufacturing of superparamagnetic magnetite-based hollow helical microdevices using cyanobacterium *Spirulina* as biotemplates (Figure 3 g-k) [61]. The fabrication sequence consisted of precursor deposition, annealing and reduction. Apart from their enhanced cytocompatibility, these microswimmers could be disassembled into small pieces upon ultrasonic stimuli, making them powerful tools for enhanced drug delivery and biodegradability.

Stimuli-responsive soft materials are currently being investigated for micro- and nanorobotics applications. The use of these materials brings the possibility of connecting the locomotion and functionalities of small-scale swimmers for specific environmental conditions. Nelson's group has reported several soft micromachines made of stimuli-responsive hydrogels [1, 62, 63]. For example, Huang et al. recently described an approach to manufacture reconfigurable soft structures such as helices and tubular heads with helical tails by means of photolithography [63] (Figure 4). The folding of hydrogel monolayers or bilayers could be conveniently predetermined through magnetic particle alignment during the fabrication sequence. The magnetic nanoparticles alignment did not only direct the folding of the hydrogel structures and enable their refolding by means of NIR heating, but also determined the easy magnetization axis of the structure. For example, under near-infrared (NIR) exposure, soft micromachines with a bilayer tubular head and a monolayer helical flagellum could change its morphology from a long slender form to a stumpy form. The long slender form consisted of a bilayer tubular head with a monolayer tail, while the stumpy morphology corresponded to a refolded tube with the flagella wrapped around the tip of the head. While both structures could corkscrew under rotating fields, the long slender form exhibited higher forward speeds than the short stumpy form. These soft micromachines offer promise for targeted drug delivery applications, in which shape plays a relevant role in both drug release and locomotion.

2.2. Flexible swimmers

By flexible swimmers, we refer to those that have either flexible tails or joints, or their entire body is bendable. Propulsion of these devices is based on their undulatory locomotion mechanism, resulting from a propagating travelling wave along their flexible parts. Magnetic flexible swimmers can be propelled by means of oscillating or rotating magnetic fields. Recently, there has been a considerable progress in the development of flexible swimmers. Dreyfus et al. were the first on describing a flexible swimmer consisting of a linear chain of superparamagnetic microbeads interconnected with double-stranded DNA fibers [64]. In order to break the spatial symmetry during magnetic actuation, a red blood cell was linked to one end of the chain. By applying oscillating magnetic fields, the swimmer exhibited a beating motion, which highly resembled the swimming pattern of eukaryotic cells such as spermatozoa.

Recently, Nelson, Pané and coworkers adopted a manufacturing procedure described by Ozin and co-workers [65] to create three-link nanowire-based swimmers (Figure 5 a) [21]. The fabrication is based on TAE, layer-by-layer deposition, and selective etching. The structures consisted of an elastic polypyrrole tail and rigid magnetic Ni links joined by flexible polymer bilayer hinges. Nanoswimmers with one, two, and three links were magnetically propelled by oscillating magnetic fields and exhibited a non-reciprocating motion. While 1- and 2-link swimmers operated as flexible oars, the 3-link Purcell-like swimmer displayed an S-like motion with the occurrence of a propagating wave.

Wang and co-workers described the fabrication and actuation of multi-segmented nanowire-based motors containing porous flexible parts by means of TAE [66]. The bendable joints were made of Ag, which was partially etched to achieve the required flexibility. A Ni segment was introduced to allow for magnetic actuation. The application of rotating magnetic fields resulted in a chiral deformation along the filaments causing the propulsion of the swimmers. More recently, Wang's group further exploited this fabrication approach to manufacture nanofish consisting of a gold head, two magnetic body segments made of Ni, and one gold segment as the caudal fin (Figure 5 b, c) [67]. These parts were linked with three flexible porous Ag joints. The work by Huang and Nelson on reconfigurable soft micromachines also describes the fabrication and motion dynamics of a swimmer consisting of a tubular head and a planar tail [63]. Interestingly, these magnetic machines exhibited higher speeds than similar types of swimmers with helical tails reported in the same work, and other propellers reported in the literature. A coupling effect between the flexible tail and the head, which increases the precession angle of the motion, is responsible for the excellent swimming performance of this microrobot.

Misra and co-workers reported the MagnetoSperm, a sperm-like micromachine consisting of an ellipsoidal magnetic CoNi head and a flexible trapezoidal tail made of SU-8 [68]. The polymer structure was fabricated by standard photolithography and the magnetic head was deposited by e-beam evaporation. The MagnetoSperm was propelled by means of oscillating magnetic fields.

Sitti's group has recently demonstrated an example of a biohybrid micromachine, which exploits microorganisms for propulsion [69]. This device consisted of a streptavidin-coated magnetic bead, on which multiple *Serratia marcescens* bacteria are attached. These bacteria propel by rotating their flagella and each provides a propulsive force of about 0.5 pN to the system. The biohybrid beads were moving in helical paths as the bacteria's propulsive force was usually exerted in an intermediate direction between the parallel and the perpendicular direction respect to the magnetization axis of the bead.

2.3 Surface walkers

Magnetic surface walkers are referred to micro- and nanorobots that move on the proximity of the surface under rotating or precessing magnetic fields. These machines can either exhibit rolling or tumbling motion with or without contact with the surface. One must note that several swimmers can become surface walkers if they are actuated close to a surface. For the earliest achievements on these types of machines, the reader is referred to the following reviews and publications [26, 70].

One of the most simple examples of a magnetic surface walker is a rotating magnetic nanowire manipulated close to a surface [10]. When the rotating plane of the nanowire is perpendicular to the surface, the interaction of the nanowire with the surface will cause a velocity difference between the two ends of the nanowire, which changes the center of rotation and results in the propulsion of the nanowire. This idea was demonstrated by Zhang et al. using Ni nanowires (Figure 6 a) [10], and adapted later to some other magnetic nanowire systems [3, 6, 71]. Taking advantage of the vortex generated by the rotating motion, surface walkers can transport and manipulate small cargos [10]. A dumbbell surface walker consisting of a Ni nanowire and two polystyrene microbeads at both ends, was developed recently to generate vortex with stronger forces, which allowed for transporting heavier or larger cargos (Figure 6 b) [72].

Ni nanowires behave as soft magnets, and their easy magnetization axis is always along their long axis, which means that under rotating magnetic fields, they always rotate about their short axis. However, this rotating model cannot generate sufficient vortices for cargo transportation. Two approaches can be adopted to fabricate microrobots able to rotate about their long axis. For example, Tung et al. fabricated a rolling microrobot – the Rodbot – by embedding a row of CoNi soft-magnetic microposts in an SU-8 cuboid with their long axis arranged perpendicular to the long axis of the SU-8 structure (Figure 6 c) [73]. In this case, the Rodbot could rotate about its long axis under rotating magnetic fields. The motion of the robot generated a rising flow and a vortex, which was exploited to transport fragile protein crystals in fluid and deposited them onto an extraction-loop without breaking them [74]. Another method consists of developing hard-magnetic structures, whose magnetic moment can be pre-defined by magnetizing them along the desired (e.g. short) axis. Chatzipirpiridis et al. fabricated such structures by electroforming hard-magnetic CoPt microtubes [75].

Other structures such as beads can be also actuated as surface walkers. For example, Chen et al. recently developed Janus micromachines, which were half-coated with $CoFe_2O_4$. The magnetically anisotropic coating allowed for the rolling motion of the Janus micromachines on a surface under rotating magnetic fields [76]. Spherical neodymium–iron–boron (NdFeB) microparticle was employed as magnetic microrobot, which can trap individual live swimming microorganism using the vortex generated by its rotation, and transport the microorganism to the desired place in 2D [77]. Colloidal particle assemblies such as doublets or wheels have also shown their potential as surface walking micromachines (Figure 6 d) [78, 79]. These structures were built through a bottom-up assembly of colloidal particles, which enabled the in-situ formation of assemblies with a variety of sizes and shapes that were easily manipulated and rapidly disassembled after use.

Surface-assisted motion can be also combined with other actuation modes to achieve different functions. For example, Hwang and co-workers developed microswimmers with multiple helical flagella to explore the possibilities of multi-modal manipulation [80]. At high operating frequencies, these microswimmers exhibited corkscrew motion with fast propulsion speeds. In this case, the machines could be employed for navigation. At low operating frequencies, the microswimmers tumbled and rolled, with low displacement speeds, and small vortex intensities. This actuation mode could be exploited for releasing the swimmers when they are blocked or stuck due to strong interactions with a surface or dust particles. Recently, Ghosh and co-workers demonstrated the independent surface-assisted magnetic manipulation of identical helical nanomotors in size and shape, but with different easy magnetization axis [81]. This method could be employed to remotely control individual machines among a swarm of nanomotors.

2.4 Other Designs

The designs of many microrobots have been inspired by the way microorganisms or cells propel. A typical example is the helical microswimmer which resembles the prokaryotic flagella and propels by transferring its rotational motion into translational motion under rotating magnetic fields. A rotating magnetic field can also be employed to actuate "microdaggers" to drill holes on cells. Srivastava et al. coated calcified porous microneedles from plant with Fe–Ti to facilitate their actuation, so that these microdaggers can be manipulated to drill holes on cells and perform site-specific drug delivery [82].

Very recently, another type of biomimetic locomotion strategy was realized on ciliary microrobots by Choi group [83]. The DLW-fabricated ciliary microrobots were designed to have a non-magnetic body and several magnetic cilia on both sides. The position and orientation control was achieved using a magnetic manipulator with non-reciprocal and stepping magnetic fields (on-off fields with a specific angle) to mimic the power stroke and recovery stroke motion.

Another interesting work reported by Faivre's group indicates that a specific shape design might not be necessary for magnetic propellers. The authors demonstrated that structures with random shapes can also be propelled by rotating magnetic fields [84-86]. The randomly shaped carbon-coated magnetic nanoparticle aggregates were synthesized by hydrothermal carbonization, an inexpensive method that allows batch fabrication [84]. Interestingly, the dimensionless speeds of these randomly shaped propellers were comparable to those of nanofabricated helical propellers. The authors also introduced dimensionless pseudochirality, a geometric parameter significantly correlated with the dimensionless speed [86]. These findings indicated that for certain applications in which precise positioning and motion are not needed, such as micromixing or environmental remediation, these reported randomly shaped propellers may be a suitable choice. The results by Faivre also suggested that there may exist some alternative small-scale machine designs to helical swimmers for certain applications.

3. The use of magnetic fields beyond propulsion

Currently, most multifunctional magnetic micro- and nanorobots only use magnetic fields for navigation or transportation, and their functions are usually triggered by other stimuli such as light, pH or heat. The realization of highly integrated multifunctional small-scale machines requires systems which could trigger different functionalities by changing on command how the energy is transferred to the devices. Magnetic manipulation, in this sense, is a very versatile approach because magnetic fields can be applied in many ways (i.e. gradients, oscillating, rotating or combinations thereof), at different frequencies, and there are several materials, which can respond differently to magnetic fields. Additionally, the shape of the device could be conveniently designed to program their response. There are some examples in the literature in which magnetic fields are not only used for navigation of small-scale devices, but also for triggering other functionalities.

Recently, Martel's group developed microrobots made of magnetic nanoparticles (MNPs) encapsulated in thermosensitive hydrogels [87, 88]. The MNPs enabled the microcarriers to travel by means of 3D magnetic gradients, along a planned trajectory in the blood vessels based on tracking information gathered using Magnetic Resonance Imaging (MRI) sequences. Additionally, these microrobots could respond to temperature changes caused by hyperthermia when exposed to alternating magnetic fields. Later, the same group investigated the influence of localized hyperthermia on the transient controlled disruption of the Blood Brain Barrier (BBB) and hence local delivery of therapeutic agents into the brain [89].

Pané and coworkers recently developed a type of micromachines by integrating magnetoelectric composite materials into the microdevices. Magnetoelectric Janus particle-based micromachines consisting of a $CoFe_2O_4$-$BaTiO_3$ core-shell bilayer structures were developed [76]. While the inner magnetic $CoFe_2O_4$ layer enables the micromachines to be maneuvered using weak rotating magnetic fields, the magnetoelectric bilayer composite provided the ability to remotely generate electric charges upon the application of alternating magnetic fields. Noble metals such as Au, Ag and Pt were magnetoelectrochemically reduced from their corresponding precursor salts and formed nanoparticles on the surface of the micromachines. These magnetoelectric micromachines are promising devices for their use as metal scavengers. A recent work by the same group demonstrated the application of hybrid magnetoelectric nanowires, composed by a magnetostrictive FeGa core and a piezoelectric polymer P(VDF-TrFE) shell, for magnetically assisted *in vitro* targeted drug delivery [71].

4. Conclusions and outlook

The last few years have seen a rapid growth in the field of magnetic micro- and nanorobots. The development of novel fabrication processes such as 3D printing or DLW has allowed for the manufacturing of complex architectures, which could not be realized by means of conventional synthetic methods. As the fabrication of micro- and nanostructures have become more flexible and versatile, fundamental theories of locomotion at low Reynolds number can now be experimentally investigated and corroborated. The simultaneous development of experimental prototypes and simulations will bring rapid optimization and will lead to ultimate designs in terms of manipulation.

On the application side, micro- and nanorobots are still in their infancy. Several challenges remain for the translation of these devices to real scenarios. For example, the manipulation of micro- and nanorobots in viscous complex fluids still requires more research efforts from the community, especially in the area of biomedical small-scale robotics. The fluids of the human body, such as blood, the cerebrospinal fluid or the vitreous humor, are often heterogeneous media composed by fibrillate microstructures (e.g. collagen, hyaluronan) and cells. A pioneering work from Nelson's group demonstrated that ABFs could successfully swim in solutions with viscosities of over 20 mPa·S (the viscosity of water is about 1 mPa·S) [90]. However, their maximum velocity is reduced due to the drastically decreased step-out frequency caused by the interactions between the ABF and the molecules in the fluid. Therefore, it is important to consider not only the macroscopic viscosity but also the interactions at micro- and nanoscales [91]. Another interesting work realized at Fischer's group successfully demonstrated that a nanoscrew with a filament diameter of 70 nm and length of 400 nm can efficiently propel in viscous hyaluronan solutions, because the size of the nanoscrew is small enough to penetrate the mesh formed by the entangled polymer chains [36]. Similar structures have been employed to demonstrate the swimming capabilities of these agents in human blood by Ghosh and co-workers [92]. A stick-and-slip motion was observed due to the colloidal jamming of the blood cells. It should be noted that the composition of bodily fluids differs substantially. Hence, successful manipulation in a certain fluid is not necessarily guaranteed in another fluid.

We have seen that small-scale machines can successfully realize mechanical jobs. In this case, the functions of micro- and nanorobots are accomplished by their mechanical actuation such as rotating, gripping, releasing, scraping, sucking, expanding or drilling, among others. Through single action or combinatorial actions, small-scale machines are able to fulfill different tasks. For example, the rotating motion of a rodbot generates a vortex, in which protein crystals can be trapped and transported (see previous section) [74]. However, to date, applications solely relying on the mechanical actuation of micro- and nanorobots are rather simple. To realize sophisticated micro- and nanorobots capable of fulfilling multiple tasks, more efforts are necessary in the fabrication and integration of building blocks.

The incorporation of smart materials in small-scale robots enables the realization of multifunctional miniaturized mobile platforms. In this case, producing highly integrated micro- and nanoagents is essentially a problem of materials science and chemistry. Stimuli-responsive materials, among others, allow microrobots to react to their environments and adapt their behaviors spontaneously. Integration of stimuli-responsive materials such as pH- or heat- sensitive hydrogels on microrobots has been successfully demonstrated, but their potential applications have not been fully explored yet. Energy conversion materials, such as magnetoelectric materials, can convert magnetic energy to other energy forms and thus induce physical/chemical/biochemical reactions. Integration of such materials enables the functionality of micro- and nanorobots to be controlled and triggered externally.

The fascinating research of magnetic micro- and nanorobots has been well established during the last two decades. While several tasks such as targeted cargo delivery, manipulation of particles and cells, detoxification or water remediation have been demonstrated, several key developments must be accomplished before translating small-scale magnetic robots to real applications: to name a few, the production of structures with more efficient locomotion in viscous fluids and high propulsion forces; the realization of environmentally friendly large batch fabrication processes with low cost and precise shape/size control in the structures and components; the development of modular systems capable of tracking micro- and nanorobots in real time, and controlling both individual agents within a group or an entire swarm; or the integration of several functional components onto a single microrobotic platform. Nevertheless, with an increasing number of researchers from various backgrounds, and by joining efforts from several disciplines, we believe that many problems and obstacles can be overcome.

Acknowledgements

This work has been financed by the European Research Council Starting Grant "Magnetoelectric Chemonanorobotics for Chemical and Biomedical Applications (ELECTROCHEMBOTS)" under the grant no. 336456.

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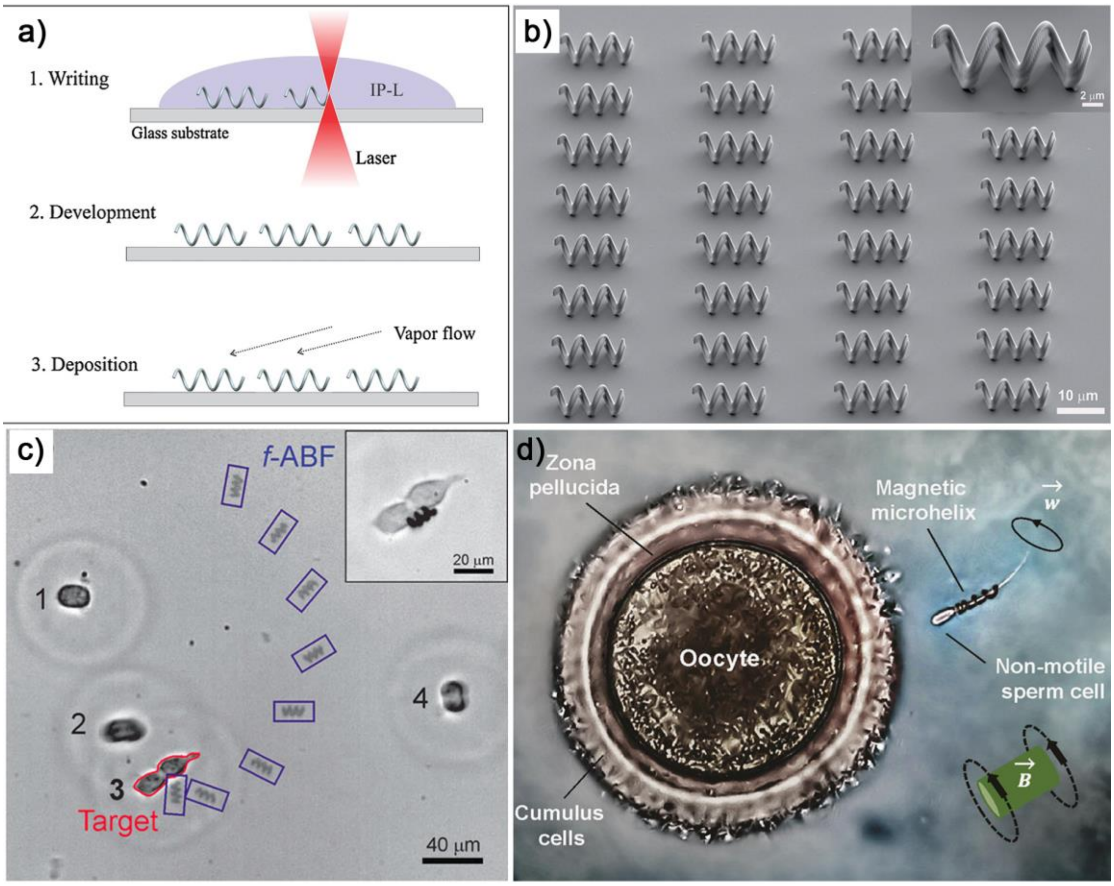

Figure 1 a) Fabrication flow of helical swimmers. Step 1-3: Direct laser writing of helical structures in photoresist; Development; Coating of Ni/Ti bilayer using E-beam deposition. Adapted from Ref. [45] with permission from Elsevier. b) SEM images of an array of helical swimmers. The inset is a magnified image of a single helical swimmer. Adapted from Ref. [44] with permission from The Royal Society of Chemistry. c) Time-lapse image of a helical swimmer moving towards a target cell. The movement of the helical swimmer was marked with blue rectangles. The inset shows the helical swimmer contacts the target cell. Copyright 2015 Wiley. Used with permission from [4]. d) A sperm is captured by a remotely controlled magnetic helical swimmer and delivered to the oocyte. Adapted with permission from Ref. [46]. Copyright 2016 American Chemical Society.

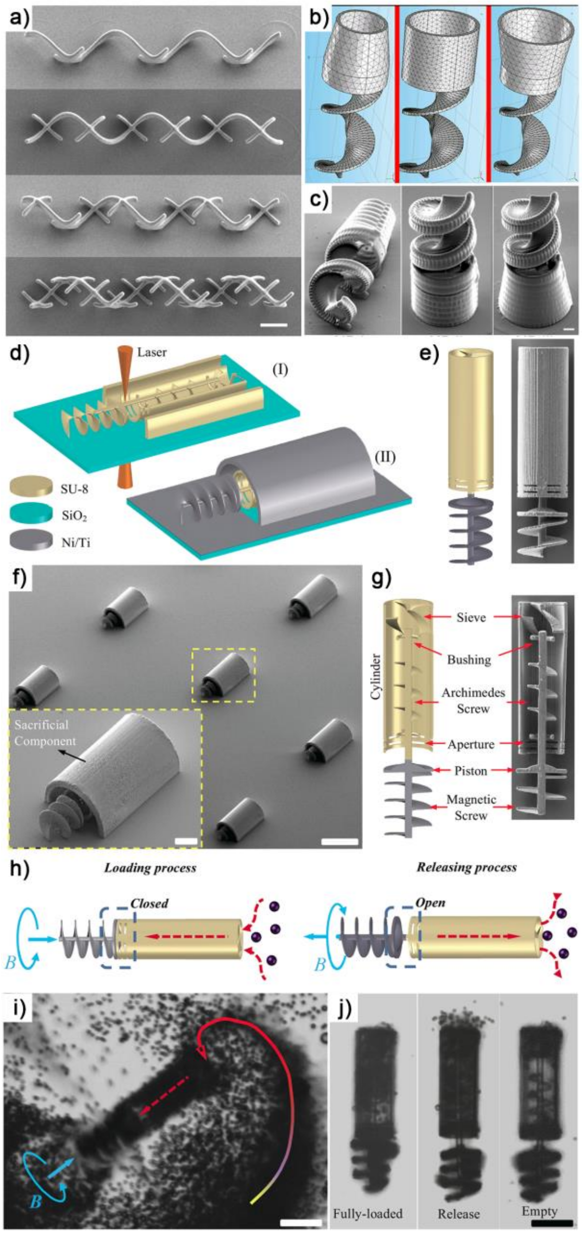

Figure 2 a) SEM images of artificial helical microswimmers with mastigonemes. The scale bar is 10 μm. b) Design and c) SEM images of 3D micro transporters. Copyright AIP Publishing. Used with permission from [48] and [49]. d) Fabrication process of compound microtransporters: (I) DLW (II) selective PVD of Ni/Ti bilayer. e) SEM image of the final device. f) An array of micromachines before removal of sacrificial structures. The scale bars are 20 and 100 μm, respectively. g) Cross-sectional view of the micromachine. h) Schematic description of the loading and releasing mechanism. i) Rotation of the screw is remotely actuated to generate a fluid flow to load microbeads into the micromachine. j) A series of images showing the release process: after the loading process, in the beginning, and at the end of the release process. Copyright 2015 Wiley. Used with permission from [51]

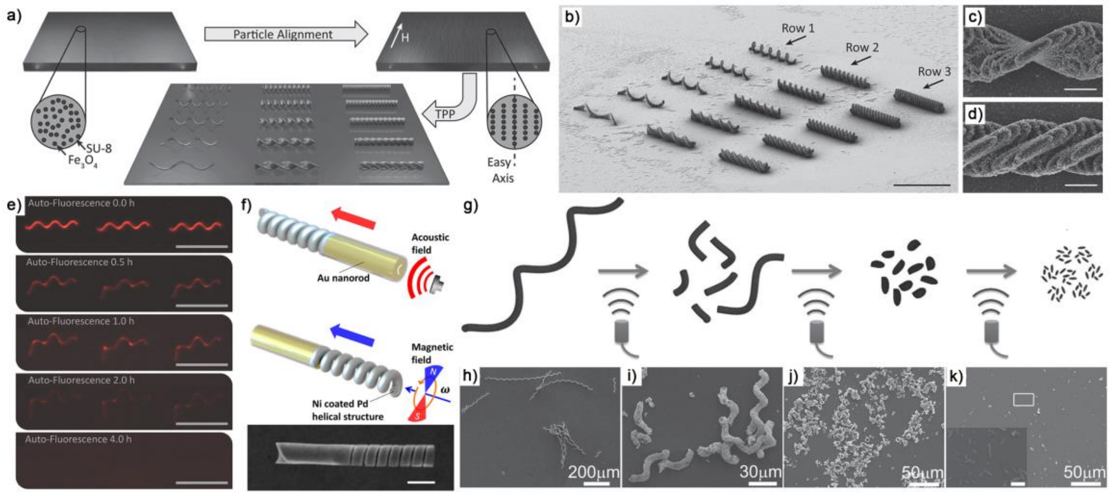

Figure 3 a) Fabrication of composite magnetic swimming microrobots. The particle distribution and, thus, the easy axis of magnetization can be controlled by external magnetic fields (zoom views). b) An SEM image of different fabricated helical microrobots. Scale bar is 50 μm; c,d) Zoomed views of different helical microrobots, scale bars: 5 μm. Copyright 2014 Wiley. Used with permission from Ref. [7]. e) Autofluorescence saponification time series of degradable superparamagnetic hydrogel swimming microrobots showing the degradation of the helical swimmers; Scale bars are 25 μm. Copyright 2016 Wiley. Used with permission from [54]. f) Schematic illustration of a magneto−acoustic hybrid nanomotor and its dual propulsion modes under the acoustic and magnetic fields; and an SEM image of a magneto−acoustic hybrid nanomotor. Scale bar: 500 nm. Adapted with permission from Ref. [57]. Copyright 2015 American Chemical Society. g) Schematic of the multilevel disassembly process of biotemplated helical swimmers with ultrasound treatment. The swimmers were fabricated by biotemplating using Spirulina as scaffolds. h–k) SEM images of the helical swimmers subject to sonication of 0, 1, 5, and 20 min, respectively. The inset is a zoomed view of the rectangle marked in (k). Scale bar: 500 nm. Copyright 2015 Wiley. Used with permission from [61].

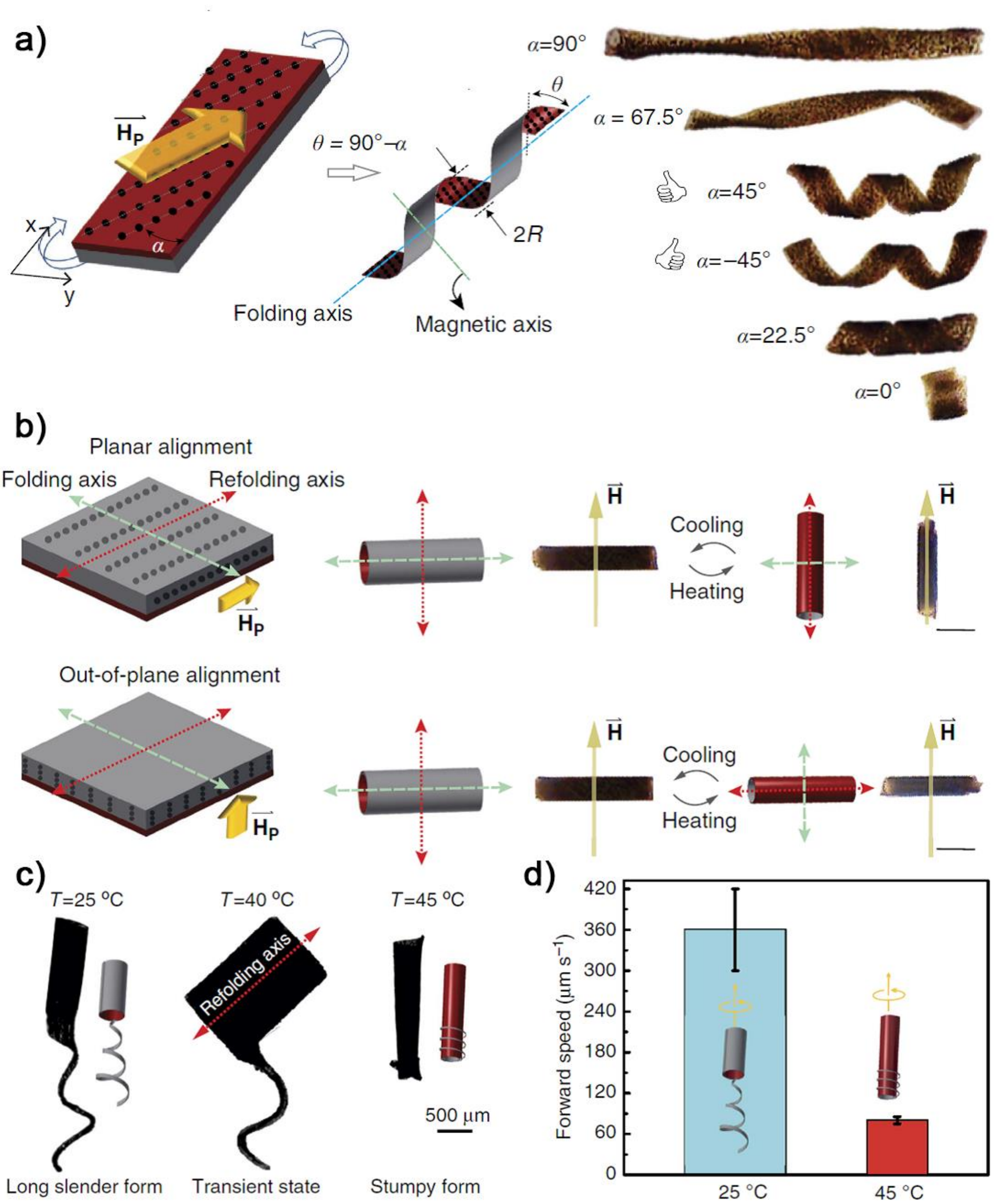

Figure 4 (a) The final shape of helical structures can be controlled by the aligned magnetic nanoparticles embedded in the hydrogel. (b) The alignment of the magnetic nanoparticles determines the magnetic easy axis of soft micromachines after they transform. While the easy axis of magnetization generated with in-plane alignment of magnetic nanoparticles can change after refolding, the magnetization in the micromachines with out-of-plane alignment remains the same. (c) A soft micromachine switches its shape between a long slender form and a compact stumpy form during heating and cooling process. (d) The forward speed of the micromachine in a long slender form is much faster than that of a compact stumpy one when it is driven with the same magnetic field [63]. Adapted with permission of Nature Publishing Group.

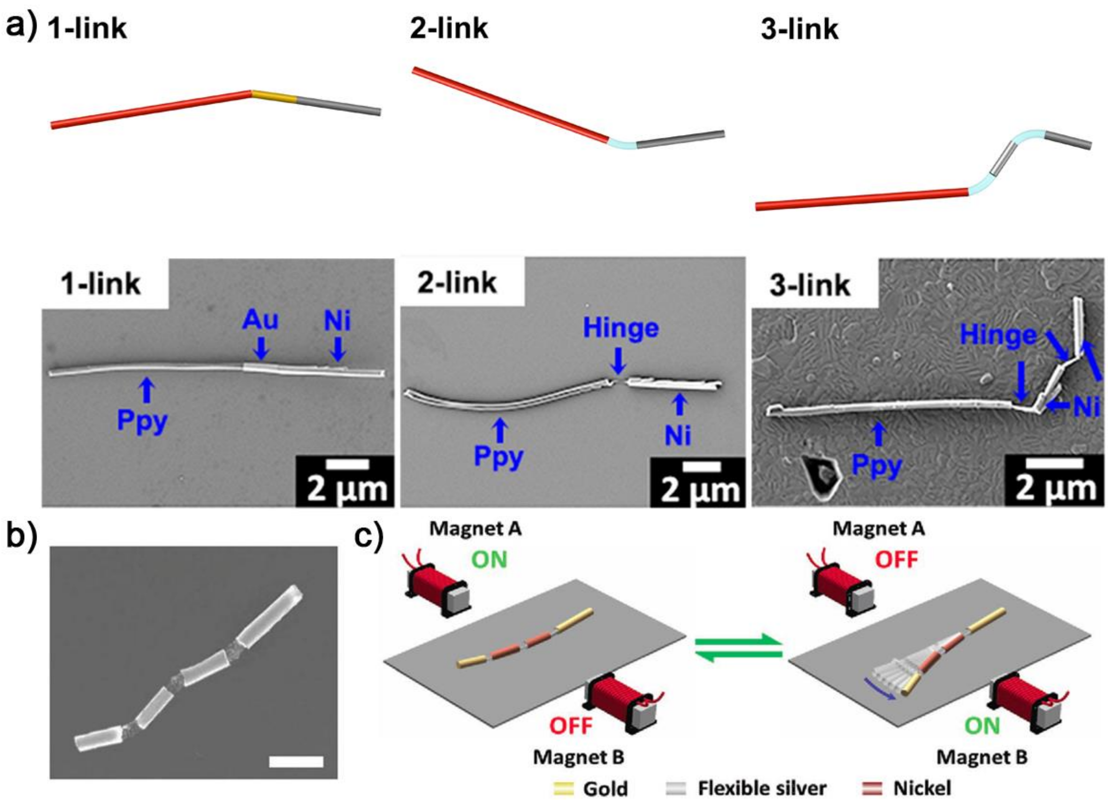

Figure 5. a) Schematic illustration and SEM images of 1-, 2-, and 3-link swimmers. Adapted with permission from Ref. [21]. Copyright 2015 American Chemical Society. b) An SEM image of a multilinked artificial nanofish. Scale bar is 800 nm. c) Propulsion of an artificial nanofish with a planar oscillating magnetic field. Copyright 2016 Wiley. Used with permission from [67].

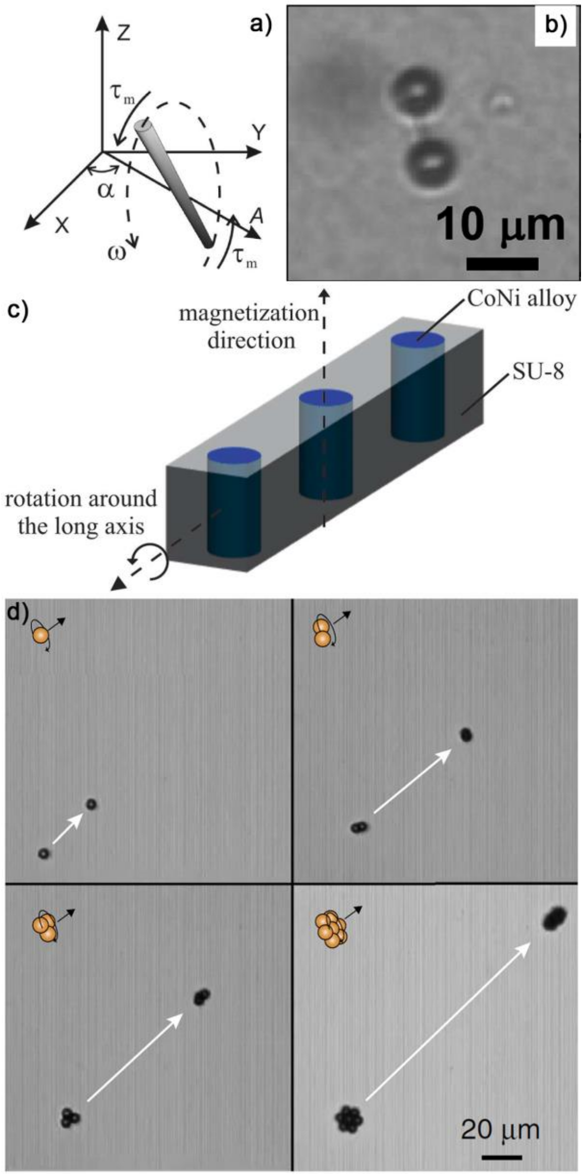

Figure 6. a) Schematic of a simple surface walker, i.e. nanowire rotating vertically with respect to the horizontal plane. Adapted with permission from Ref. [10]. Copyright 2010 American Chemical Society. b) An optical image of a magnetic dumbbell assembled by a Ni nanowire and two PS microbeads. Copyright 2016 Wiley. Used with permission from [72]. c) An illustration of a RodBot [73]. Reproduced with permission of the International Union of Crystallography. d) Translational movement under identical rotating magnetic fields demonstrates that larger wheels roll farther in a given time span [79]. Adapted with permission of Nature Publishing Group.