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MEMS Actuators for Biomedical Applications: A Review

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Abstract

Micro-electromechanical-system (MEMS) based actuators, which transduce certain domains of energy into mechanical movements in the microscopic scale, are increasingly contributing to the areas of biomedical engineering and healthcare applications. They are enabling new functionalities in biomedical devices through their unique miniaturized features. An effective selection of a particular actuator, among a wide range of actuator types available in the MEMS field, requires to be made through assessment of many factors involved in both the actuator itself and a target application. This paper presents an overview of the state-of-the-art MEMS actuators that have been developed for biomedical applications. The actuation methods, working principle, and imperative features of these actuators are discussed along with their specific applications. An emphasis of this review is placed on temperature-responsive, electromagnetic, piezoelectric, and fluid-driven actuators towards various application areas including lab-on-a-chip, drug delivery systems, cardiac devices, and surgical tools. It also highlights the key issues of MEMS actuators in light of biomedical applications.

Keywords: MEMS, actuators, biomedical devices, lab-on-a-chip, smart implants, surgical devices

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1. Introduction

The rapid development of micro-electromechanical-system (MEMS) technologies has increasingly provided means to miniaturize and advance various biomedical devices and bioMEMS [1-4]. The applications of these MEMS-based devices include cardiac devices [5, 6], microneedles [7, 8], lab-on-a-chip devices for fast chemical/biological analysis [9-11], microsurgical robots [12-16], and *in-vivo* drug delivery systems for drug release with precision dosage and timing control [17-20]. MEMS actuators are widely used to realize these types of devices and enable accurate control of them [21]. Serving as core architectural elements, MEMS actuators have emerged as a promising technology that plays a vital role in enabling a wide range of biomedical devices. Among existing MEMS actuators, those with thermoresponsive [22], electromagnetic [23], piezoelectric [24], thermopneumatic [25], and pneumatic [26] mechanisms have been some of the representative types widely used for biomedical applications. Each of these actuator types possesses attractive features. For instance, shape memory alloys (SMAs), a type of smart materials that respond to temperature, offer high work density, large actuation force and displacement, simple structural design, resistance to corrosion, and biocompatibility [27-29]. Electromagnetic actuators generally provide large displacement, fast dynamic response, and an ability of low-voltage and remote actuation [30-32]. Piezoelectric actuators are often used in ultra-precision and high-speed applications due to their ability of nano-scale actuation, quick response, and self-locking at power-off state [33-36]. Pneumatic microactuators are well-known for simple structure, high flexibility, high force per unit volume, high energy density, and low cost [37-41].

The capabilities of MEMS actuators are continuously growing with a great promise for diverse future applications. As those actuators exhibit different characteristics and shortcomings, however, a particular type should be wisely selected and applied for a targeted biomedical device while assessing the requirements involved in the device and its environment. In this paper, the working principles, designs, characteristics, and their key applications of MEMS actuators are comprehensively discussed with an aim to aid further development of bioMEMS and other biomedical microdevices functionalized by the actuators. This review is structured as follows: The working principles of thermoresponsive, electromagnetic, piezoelectric, and fluid-driven microactuators are discussed in Section 2. Section 3 presents critical applications of these actuators, including lab-on-a-chip, drug delivery systems, cardiac devices, and surgical and endoscopic tools. The review is concluded with a discussion of major factors toward enabling elevated performance of these actuators in Section 4.

2. Types of Biomedical MEMS Actuators

2.1. Thermoresponsive Actuators

SMAs, shape memory polymers (SMPs), and certain types of hydrogels are classified as smart materials that have an ability of shape recovery when triggered by an environmental stimulus. They commonly respond to heat, whereas specific responsive hydrogels also trigger with others such as radiation, moisture, pH level, and magnetic and electric fields [42-47]. This section reviews these thermoresponsive smart materials regarding their phase transition modes and characteristics that allow them to work as actuators in the micro domain.

2.1.1 SMA

The actuation of SMAs is based on the principle of a shape-memory effect called martensitic-austenitic transformation. When a SMA is in its martensite phase, the alloy is in the form of monoclinic crystals, which makes it more flexible and hence more easily deformed. Following the deformation of the material's crystalline orientation, cubic crystals are constructed within the molecular arrangement, while the material becomes rigid and hard to deform above the austenite temperature upon heating. When a SMA is cooled in the absence of a load, the materials crystal structure follows twinned martensite. During this phase, the SMA can be deformed by applying an external force or by employing a bias spring to achieve reversible motion. The changes in the crystalline state of SMA are illustrated in Figure 1a [48]. There are several phase transformation temperatures that must be considered when selecting a SMA with respect to its applications. During the shape recovery process, the transformation from the martensite cold state to the austenite hot state begins at the austenite starting temperature and ends at the austenite finishing temperature. Meanwhile, the transformation from the hot austenite phase to the cold martensite phase begins at the martensite starting temperature and ends at the martensite finishing temperature. The SMA typically consists of a few elements, and the composition level among these elements determines the transformation temperature. In other words, the elemental composition can be adjusted to achieve a specific transformation temperature depending on the application.

SMA actuators in the MEMS area are typically fabricated in a form of patterned thin film or bulk-micromachined structures [49-59]. They possess general attractive attributes

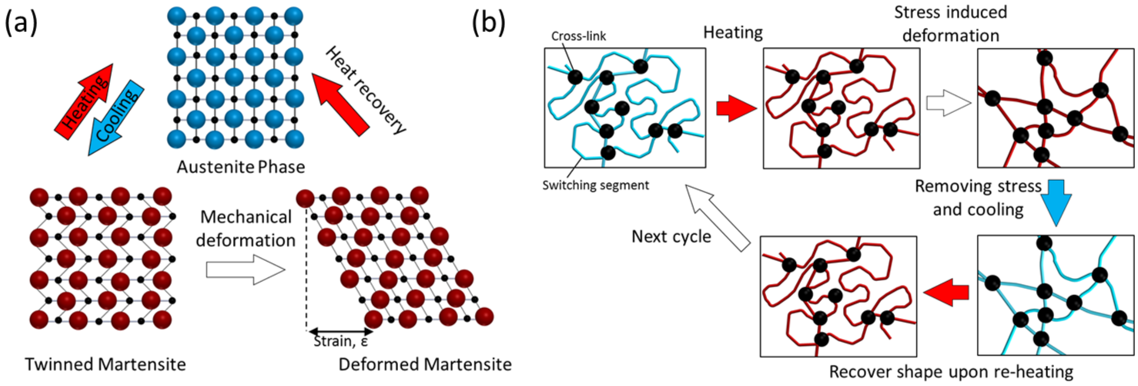

Figure 1. Phase transformations of shape-memory materials. (a) Changes in the crystalline orientation of SMA at different phases. Reproduced with permission [48]. Copyright 2016, Elsevier. (b) Shape recovery process in SMP. Reproduced with permission [76]. Copyright 2016, Wiley-VCH.

including large displacement, large force, high mechanical robustness, and corrosion-resistant [60-66]. The NiTi alloy known as Nitinol is one of the most widely used SMA materials for biomedical applications owing to its high biocompatibility that facilitates the application for implantable devices such as surgical tools, cardiac devices, and drug delivery systems [22, 56, 67-71]. General disadvantages of SMA actuators lie in relatively slow temporal response as well as high power consumption when actuated with self-heating by passing an electrical current to the material.

2.1.2 SMP

The SMPs have gained significant interest in biomedical applications due to its general features such as structural flexibility, large strains, low density, tunable transition temperature, and biodegradable properties [72, 73]. These features make them suitable for applications in endovascular and drug delivery devices [74, 75]. The thermoresponsive SMP exhibits a shape-memory effect based on the polymer’s dual-segment system comprised of cross-links and switching segments. The cross-links determine the permanent shape of the polymer whereas the switching segments coupled with transition temperature fix the temporary shape. The SMP is stiff when its temperature is below the transition temperature, whereas heating it over the transition temperature makes it relatively soft. For shape setting, an external force must be applied to an SMP while it is heated above the transition temperature. This step causes the switching segments to fix the molecular chain positions. Afterwards, the SMP is cooled while removing the external force to result in a memorized shape for the polymer. Applying heat to the SMP induces recovery of the memorized shape through the shape memory effect as illustrated in Figure 1b [76]. Although this actuator possesses the aforementioned beneficial properties, SMPs often suffer from slow response and low recovery stress.

2.1.3 Temperature-Sensitive Hydrogels

Hydrogels are three-dimensional polymeric networks with hydrophilic structures that allow the absorption of a large amount of aqueous solution in the networks [77]. Depending on the type of cross-linking between polymers, some of them display mass reversible changes in response to physical or chemical stimulus [77]. Poly(N-isopropyl acrylamide), or PNIPAM in short, is a thermoresponsive hydrogel that changes its size at a phase transition temperature called the lower critical solution temperature (LCST) in the solution [78]. When temperature of PNIPAM hydrogel is raised above the LCST, the material shrinks by releasing the uptake solution, whereas reducing the temperature reverses the process [79]. Different material compositions of PNIPAM can be used to modify its LCST level to tailor it to a specific application [80]. Besides intrinsic phase transition behavior, the hydrogels also possess distinct attributes such as tunable mechanical and degradation features, sensitivity towards stimuli, and ability to conjugate with hydrophilic and hydrophobic therapeutic compounds. Additionally, PNINAM can be synthesized to be ultraviolet-light sensitive in its polymerization, which enables precise patterning and complex structure formation of the polymer through a photolithographic process [81]. These features have promoted the application of PNIPAM for biomedical devices, such as microvalves in drug delivery systems as well as encapsulation and delivery of cells [79, 82-90]. In spite of many advantages, thermoresponsive hydrogels inherently suffer from relatively slow temporal responses similar to SMA and SMP, and may pose leakage of the solution through the material.

2.2 Electromagnetic Actuators

Electromagnetic actuators generally employ the interaction of one or more magnetic structures with the magnetic field (B) produced by a current-carrying circuit [91]. A common configuration of these actuators consists of a coil and a ferromagnetic movable structure placed in the field produced by the coil as illustrated in Figure 2 with a suspended cantilever beam being the movable magnetic structure [92, 93]. When the driving current, i, is passed through the coil, it produces B defined by Biot-Savart law [94, 95] as:

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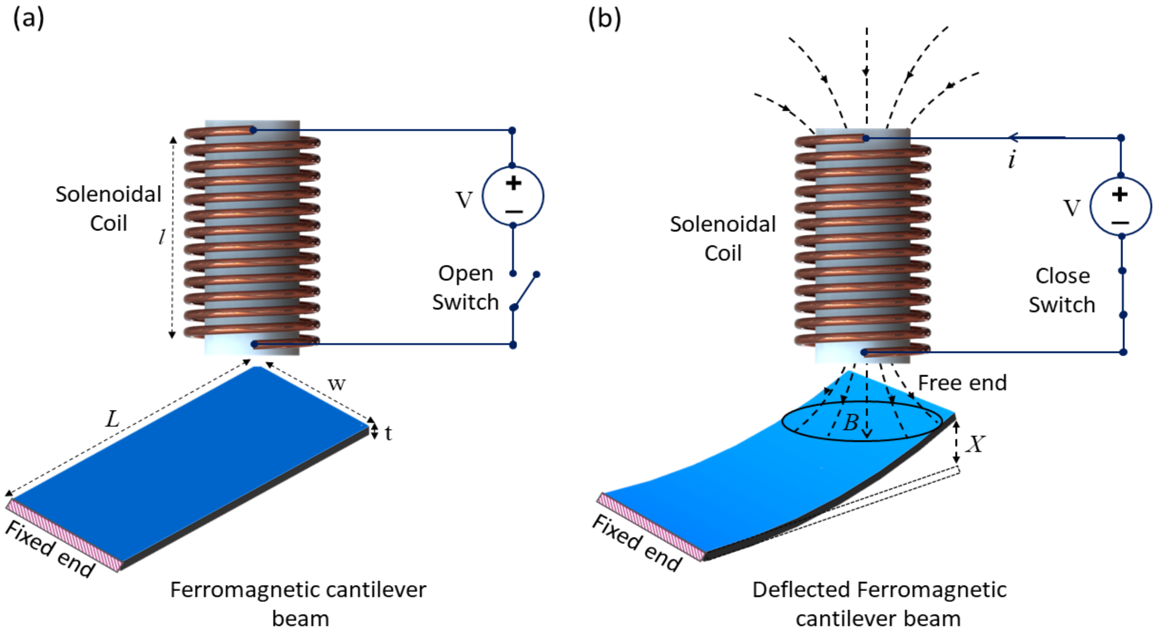

Figure 2. Schematic diagram on the working mechanism of an electromagnetic actuator under (a) the off state without current and (b) the on state with a driving current fed to the solenoidal coil creating a magnetic field to displace the ferromagnetic movable microstructure.

$$B = \mu_0 \mu_r \frac{N_i}{l} \tag{1}$$

where μ_0, μ_r, N_i, and l are the permeability of free space, the relative permeability of the material, the number of the coil's turns, and the length of the coil, respectively. The interaction with B induces an attractive force, F, acting on the cantilever beam to cause a displacement, X, at the beam's free end, which can be expressed as [96]:

$$X = \frac{12FL^3}{8Ewt^3} \tag{2}$$

where L, E, w, and t are the length of the beam, the Young's modulus of the material, the width of the beam, and the thickness of the beam, respectively. This type of actuators has been used in various MEMS applications given its advantages such as simple drive mode, high field energy density, fast response time, and large deflection that are attainable with low input voltages [31, 32]. Their applications extend to micro positioning systems [97], micromirrors [98, 99], micrograppers [100], and microfluidics [23, 101] for micropumps [102, 103] and microvalves [104]. Electromagnetic actuators also exhibit common disadvantages, e.g., volumetric scaling of produced electromagnetic forces that rapidly drop

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as the device size shrinks, high power dissipation for driving coils, and parasitic loss at high frequency [105], which should be taken into account in the design of application device.

2.3 Piezoelectric Actuators

Piezoelectric actuators have been widely adopted in the fields of ultra-precision engineering and microactuation owing to its advantageous features such as fast response, high displacement resolution, high efficiency, compact structure, and immunity to magnetic field [34, 106-108]. The operation of the actuators relies on the converse piezoelectric effect of a piezoelectric crystal to induce strain by applying an electric potential to the crystalline material [109]. The converse piezoelectric effect can be theoretically described with the following relationships [110]:

$$S = s^E T + dE \tag{3}$$

$$D = dT + \varepsilon^T E \tag{4}$$

where S, E, s^E, T, D, d, and ε are the strain, the electric field, the compliance with zero field, the surface stress, the charge displacement, the piezoelectric strain coefficient, and the dielectric constant of a piezoelectric material, respectively. The performance of this type of actuators largely depends on the crystal structure of a piezoelectric material where d acts as a medium for the transduction mechanism. Given the orientations of polarization and electric field (P and E, respectively), three different modes, i.e., longitudinal mode (d_{33}), transversal mode (d_{31}), and shear mode (d_{15}) define the actuation of the material. Figure 3a shows the piezoelectric actuation mode with the six orientations of the coordinate systems (x, y, z, θ_x, θ_y, and θ_z) and the polarization of a single layer piezoelectric crystal under P. For d_{33} and d_{31} modes, E applied parallel to P results in a longitudinal deformation (δ_h) and a transversal deformation (δ_l) simultaneously (Figure 3b), whereas E is perpendicular to P for d_{15} and produces shear deformation (δ_s) (Figure 3c) [111]. Among these modes, d_{33} and d_{31} provide higher strains than d_{15}. Piezoelectric actuators produce small strains in an accurate and fast manner, and thus have been used for a variety of high-precision actuation applications such as micro/nano-positioning systems [112, 113], micropumps [114, 115], and micro-robotics [116]. In spite of their advantages, incorporation of piezoelectric materials such as lead zirconate titanate (PZT) and lead magnesium niobate-PZT ceramics in MEMS fabrication is often challenging due to the need for high-temperature thermal processes and the instability of deposited materials [117, 118]. Besides, the need for relatively high driving voltages and

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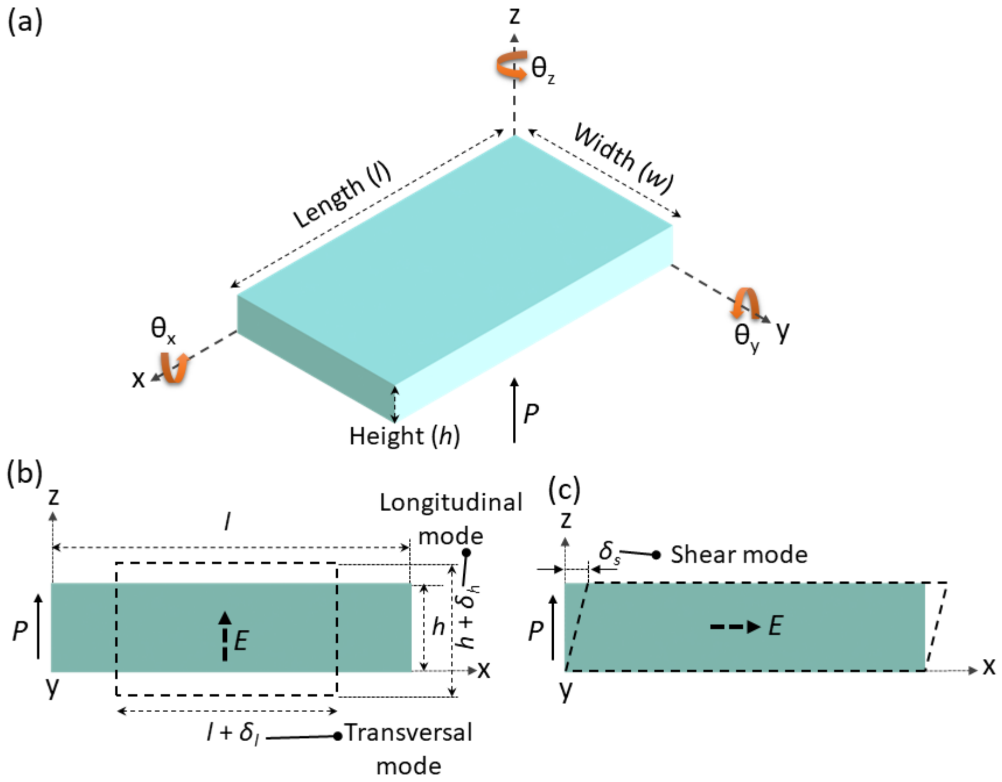

Figure 3. Piezoelectric actuation modes: (a) Orientations of the actuation field and polarization field; (b) longitudinal and transversal modes; (c) shear mode.

the large hysteresis/nonlinearity are other factors that can limit their application range [105, 119, 120].

2.4 Fluid-Driven Actuators

Soft and flexible actuators have been attracting attention for biomedical applications as tissue interaction with mechanically rigid actuators could lead to damage to the tissue. In this context, many studies have looked at hyperelastic-material-based pneumatic and hydraulic actuators. These types of actuators are typically comprised of fibreless or fibre-reinforced polymeric channel structures that allow for supply of gas or liquid (typically air or water, respectively) to the channels [121] (e.g., McKibben artificial muscle [122]). Once fluidic pressure is applied to the actuator's channel, it causes elastic deformation in its overall structure, resulting in a designed mode of actuation such as expansion, contraction, bending or twisting motions [123, 124]. For example, pneumatic actuators having symmetric cross sections expand or contract, while those with asymmetric cross sections (created by, e.g., bonding two flexible layers with different wall thicknesses or stiffness levels), such as

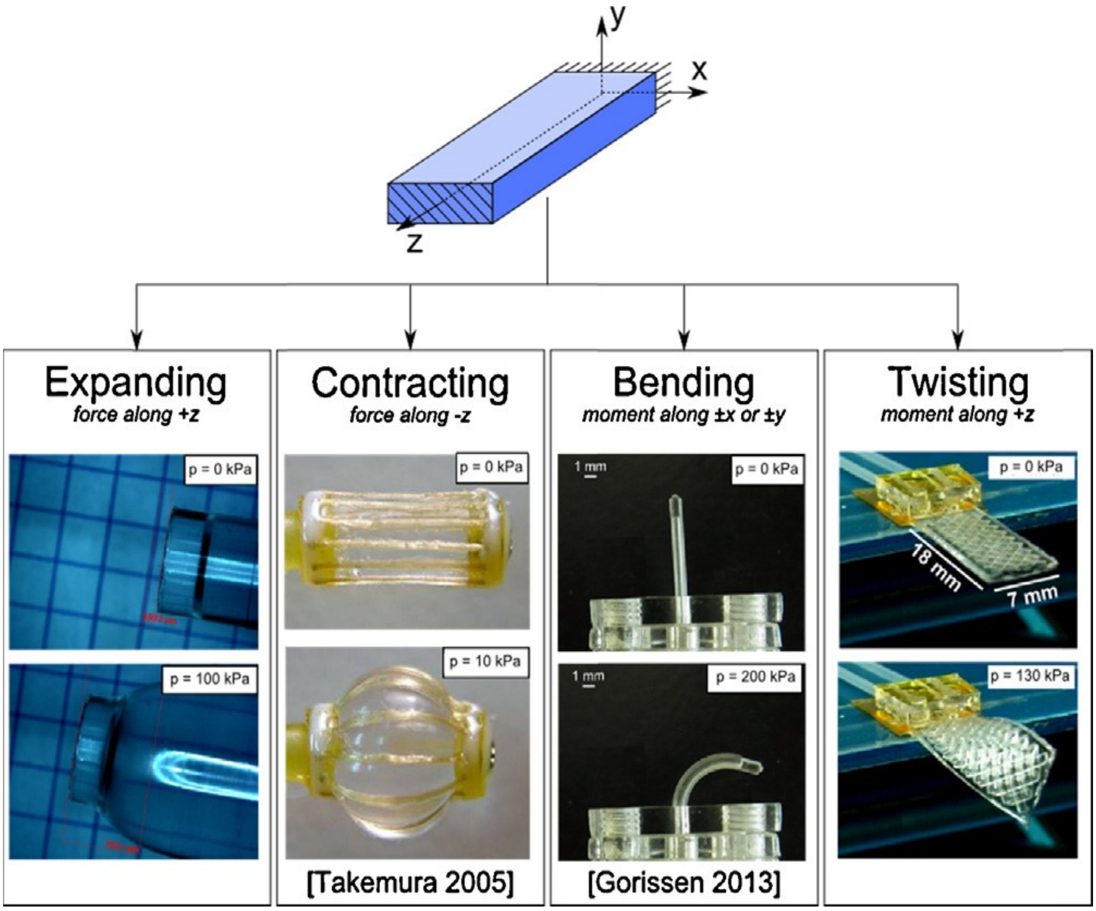

Figure 4. Overview of flexible pneumatic actuators showing four different actuation modes. Reproduced with permission. [127] Copyright 2014, Elsevier.

pneumatic balloon actuators (PBA), show bending deformations [125]. Likewise, two arrays of PBAs combined in the opposite bending directions cause twisting motions (Figure 4) [126, 127]. In addition, the pneumatic actuator with a single or dual-channel structure can produce bidirectional curling or bending motions, respectively [128-131], while a three-channelled pneumatic soft actuator offers bending motions in up to six different directions [132]. Based on these features, Suzumori *et al*. developed a flexible microactuator having three chambers for pneumatic supply [133, 134]. The actuator had a cylindrical fibre-reinforced rubber structure that provided 3-degree-of-freedom motions. Another study investigated a MEMS-based hydraulic actuator based on a finger-shaped chamber structure for its actuation, which used an integrated heater to pressurize the fluid through its thermal expansion [135]. The fluid-driven actuators offer advantageous features such as high flexibility, large displacement, biocompatibility (when fabricated/coated with biocompatible materials), lightweight, high power-to-weight ratio, simple/low-cost fabrication [136, 137], which makes them suitable for applications in medical and surgical devices, whereas the need for means of fluid supply and pressurization, actuation precision, and miniaturization are general areas of limitations.

3. Biomedical Applications of MEMS Actuators

This section emphasizes the applications of the aforementioned actuators in biomedical areas with a focus on lab-on-a-chip, drug delivery systems, cardiac devices, and surgical tools. The key functions of reported devices and the particular contributions of microactuators to them are discussed.

3.1. Lab-on-a-Chip (LoC)

LoC is a class of miniaturized microfluidic devices configured in a single-chip form that is primarily designed for biological or chemical processing and analysis [138]. These devices allow miniaturization and amalgamation of complex processes to be implemented on a small chip, which otherwise needs to be operated via repetitive laboratory tasks. The key features of these devices include compactness/portability, dramatic reduction of required chemicals and samples, higher process controllability, and faster analysis. The parallelization of many functions integrated on LoC is leading to an emerging trend in point-of-care diagnostics [139]. LoC devices are functionalized by forced fluid flow through microfluidic channels patterned on them. To control flow sequence, duration and timing, direction, and flow rate of each fluid being processed, micro-scale pumps, and valves are integrated with the channels on the chip, allowing for precise on-chip manipulation of small quantities of particular fluids.

Piezoelectric actuators have been one type of the actuators widely used as micropump elements in LoC to control the fluid flow with high accuracy. For example, a multi-chamber piezoelectric pump was reported to control the fluid flow rate [140] (Figure 5a). As a sinusoidal signal was applied to the actuator, the chamber expanded and opened the valve, causing the fluid flow based on the inverse piezoelectric actuation. For point-of-care testing and chemical analysis, a plug-and-play microfluidic chip integrated a piezoelectric peristaltic micropump was demonstrated [141]. The fluid in the microchannel was transported through impacting actions provided by the piezoelectric actuator (Figure 5b). In order to enhance the functionality and performance of LoCs, researchers have also incorporated surface acoustic wave (SAW) driven piezoelectric actuators into the LoCs to precisely control fluid flows and microparticles. SAW based actuators are advantageous in LoCs owing to their features such as low cost, simple fabrication, fast actuation, high adaptability, contact-free particle

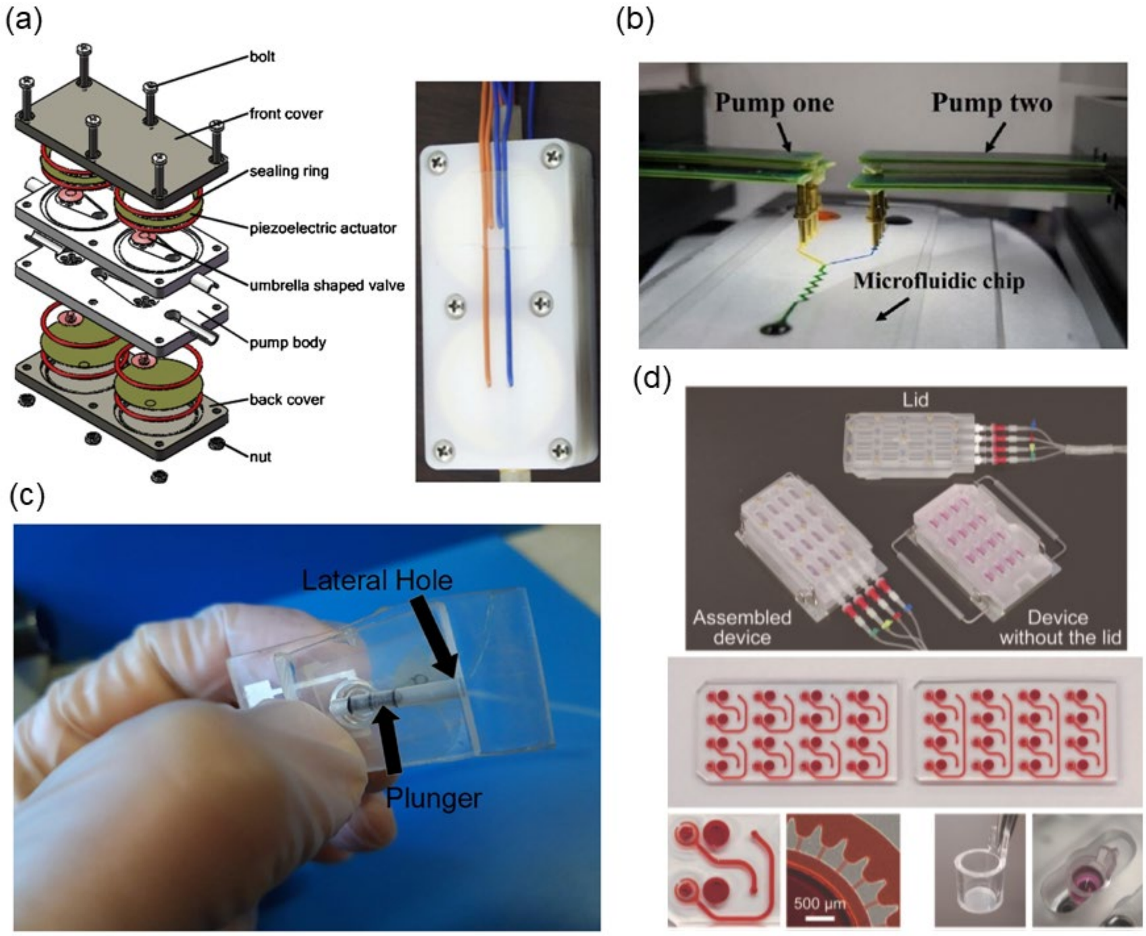

Figure 5. LoC systems and their components. (a) Schematic and prototype of a piezo-actuated pump. Reproduced with permission [140]. Copyright 2019, Elsevier. (b) Piezoelectric-actuator-based microfluidic pump module. Reproduced with permission [141]. Copyright 2019, Elsevier. (c) Thermopneumatically actuated microchamber. Reproduced with permission [144]. Copyright 2019, Elsevier. (d) Pneumatically driven multi-organ-on-a-plate system, showing (top) culture device, (middle) microfluidic plates, (bottom left) culture unit and Laplace valves, and (bottom right) membrane insert and culture chamber. Reproduced with permission [145]. Copyright 2019, RSC publishing.

manipulation, and biocompatibility [142]. For instance, Ding *et al.* demonstrated standing SAW based acoustic tweezers to trap and manipulate single microparticles, cells, and organisms in a microfluidic chip. These tweezers were shown for real-time manipulation of microparticles by utilizing a wide resonance band of interdigitated transducers [143]. For the fluid-driven actuation approach, a LoC based on thermo-pneumatic actuation was reported to control the flow rate inside the microfluidic channel (Figure 5c) [144]. In addition, a multi-throughput multi-organ-on-a-chip system was developed by utilizing a pneumatic actuator

(Figure 5d) [145]. This device could handle eight different conventional cell culture experiments (including cell seeding, medium change, live/dead staining, cell growth analysis, and gene expression analysis of collected cells) at a time offering a potential for drug discovery applications.

Electromagnetic actuators are another group that has been employed in micropump and microfluidic applications exploiting their favorable features for LoC such as rapid response, large force, and low-voltage operation. For instance, Pradeep *et al.* developed an electromagnetically actuated valves to control multiple fluid flow on a programmable microfluidics platform (Figure 6a) [146]. The device was comprised of polydimethylsiloxane (PDMS) based microfluidic channels and membranes with an electronic board that held solenoids. The activation of the solenoid attracted the valve to deflect the PDMS membrane, which in turn created a path for fluid flow. Another electromagnetically actuated micropump was reported to provide bidirectional flow [147]. This device used two pairs of power inductor and NdFeB magnet (Figure 6b), in which the two magnets were synchronously

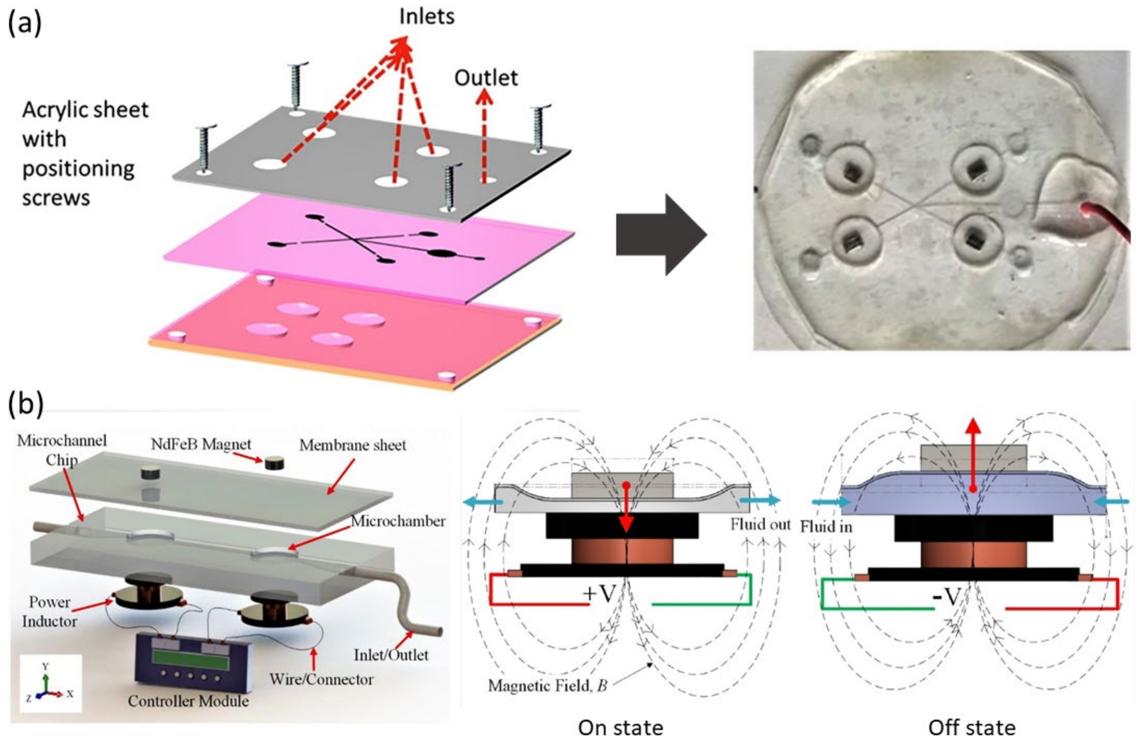

Figure 6. Electromagnetically actuated microfluidic devices. (a) Schematic and image of fabricated microfluidic channel with active valves. Reproduced with permission [146]. Copyright 2018, Elsevier. (b) Schematic diagrams of (left) a dual-chamber micropump and (right) operating principle of the actuation with positive and negative driving voltages. Reproduced with permission [147]. Copyright 2018, Elsevier.

actuated under either attractive or repulsive condition (by switching the polarity of voltage applied to the inductors) to pump the fluid inside the channel in either direction. In another example, Tahmasebipour *et al.* fabricated an electromagnetic uni-/bi-directional diffuser micropump, which used the magnetic membrane based on a PDMS-Fe_3O_4 nanocomposite for its electromagnetic actuation to create fluid flow through microchannels [148]. These micropump devices could be employed in various microfluidic and LoC devices.

3.2. Implantable Drug Delivery Systems

Advances in MEMS and miniaturization technologies have enabled implantable biomedical devices specifically designed to assist in the diagnosis and treatment of chronic or acute diseases. Micromachined drug delivery systems are among those emerging implantable devices. Many of these systems are comprised of micro reservoirs that store liquid-phase drugs and microactuators that constitute a mechanism to eject the drugs out of the systems and deliver them to the implanted sites [149]. Aside from the significant improvement in bioavailability of drugs, the advancement of this type of systems is expected to enable patient-tailored, pin-point treatments of targeted diseases such as cancer, diabetes, and osteoporosis, while significantly reducing *in-vivo* invasiveness of the systems due to their miniaturized forms.

MEMS drug delivery systems use microvalves to channel/regulate the drug flow into the diseased location [150]. Thermoresponsive hydrogels have been often used to form smart microvalves in them [84, 86, 151-156]. A study reported an implantable drug delivery device that was fabricated to integrate PNIPAM microvalves with a wireless resonant heater and a drug reservoir [84]. The microvalves were patterned using an *in-situ* photolithography technique and were wirelessly operated by activating the resonant heater using a tuned external radiofrequency (RF) field. This hydrogel microvalve demonstrated 38% shrinkage in its size upon activation that allowed for release of test drug from the reservoir. Another drug delivery system using a thermoresponsive hydrogel valve was reported to demonstrate its repeatable drug release mechanism controlled by induction heating [152]. This device showed the release of drug as well as its reverse flow to refill the reservoir. A more comprehensive study on drug delivery through a MEMS device using reversible or irreversible polymeric valves reported reproducible release control utilizing hydrogel-based artificial muscle [153]. Eddington *et al.* developed a drug delivery device by employing an array of pH-sensitive hydrogels (Figure 7a) [154]. Besides above efforts, various studies have reported hydrogel-based microvalves that could be applied to MEMS-based drug delivery [155-159]. As a different approach, piezoelectric microvalves have also been studied for the same purpose. This was demonstrated, for example, in a study that developed a wirelessly controlled normally-closed piezoelectric microvalve activated by an inductor-capacitor (LC) resonant circuit (Figure 7b) [160]. The activation of the LC circuit required the field frequency to be modulated to 10 kHz resonant frequency that matched the optimal operating frequency of the device.

Micropumps are another essential element for MEMS drug delivery systems to transport drugs from the reservoirs to the outlets of the systems. SMA, thermopneumatic and piezoelectric actuators have been among those often used in micropump-driven systems. An implantable drug delivery chip reported in [70] integrated an SMA-based micropump for the release of stored drug from the chip. The SMA was bulk-micromachined to form a resonant circuit, which served as a self-heat source activated by RF power transfer to allow frequency-selective actuation and pumping of drug out of the chip. Thermopneumatic micropumps based on a similar powering method were developed for release control [161], including multiple drug delivery and mixing with a zigzag micromixer [162]. Piezoelectric actuated micropumps were also reported for implantable drug delivery applications [163, 164]. Besides, a polymer-based reusable implantable drug delivery system with refillable functionality was developed [165]. This device was designed to provide control and refillable functionalities for broad drug compatibility. Some of the implantable drug delivery systems were reported to integrate SMP actuators [72, 166, 167]. For example, studies reported the SMP-pumped implantable device operated by external RF magnetic fields with an actuation range of 140μm using a 50-mW RF power and showed an average release rate of 0.172 μL/min [72, 166]. A chemotherapy drug release system was realized using hydrolytic degradable SMPs and was evaluated in the impact of the drug release profile [167]. Apart from the actuation mechanisms discussed above, electrochemically driven micropumps have been shown in several reports [168-171]. These studies integrated an electrochemical bellow actuator, transcutaneous cannula, and a dual regulation valve to form an implantable drug delivery device [168], showing *in-vivo* implementation for anti-cancer drug delivery through wireless powering [169], and demonstrated similar devices for controlled delivery of boluses from the fabricate prototypes (Figure 7c) [170, 171].

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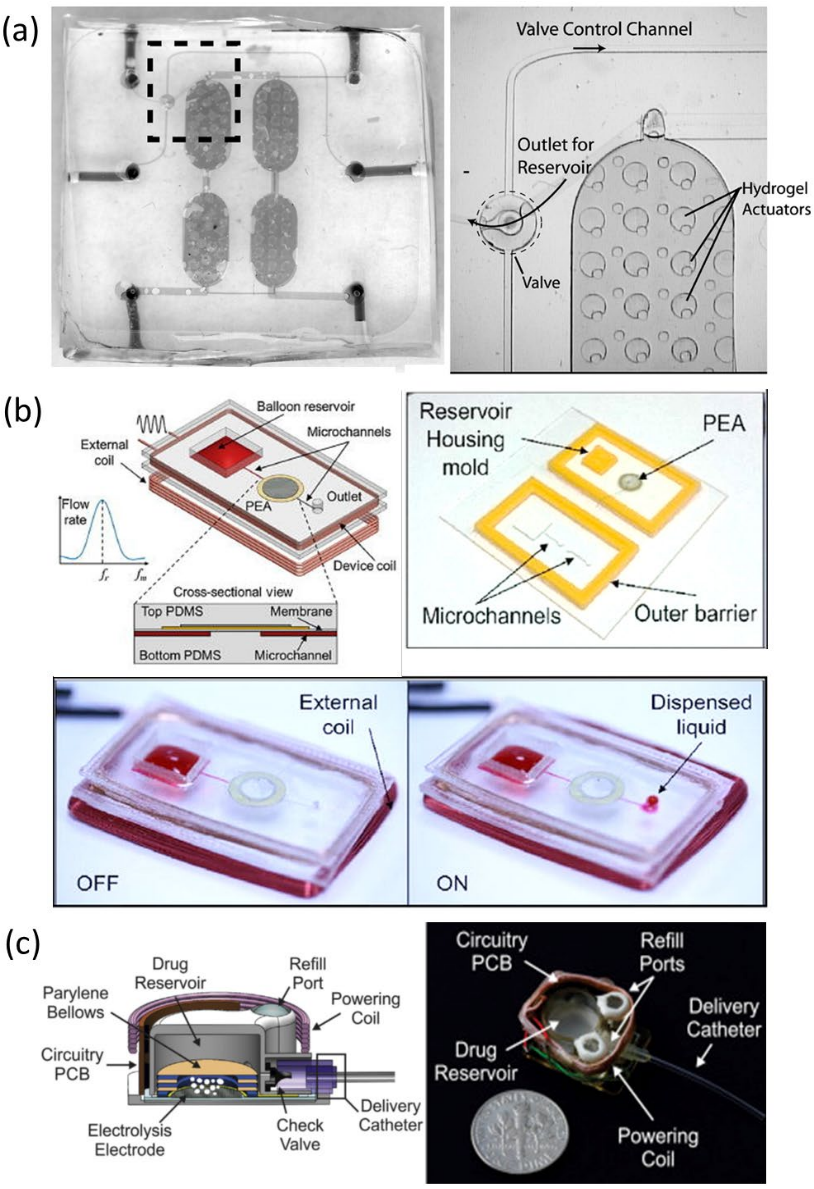

Figure 7. Drug delivery microsystems: (a) (Left) complete microfluidic device and (right) integrated array of hydrogel actuators. Reproduced with permission [154]. Copyright 2004, IEEE. (b) (Top left) schematic and cross-sectional diagrams of the device, and fabrication results showing (top right) top and bottom molds and (bottom) device under off and on states. Reproduced with permission [160]. Copyright 2018, Elsevier. (c) (Left) schematic diagram and (right) fabrication result of wirelessly powered electrochemical bellow micropump. Reproduced with permission [171]. Copyright 2016, Elsevier.

3.3. Cardiac Devices

Many implantable devices are targeted at providing enhanced diagnoses and/or therapeutic treatments for specific diseases *in vivo*. Cardiac implants are a good example of them.

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Atherosclerosis is a type of cardiovascular disease where arteries become hardened and narrowed due to plaque build-up on their inner walls. In conjunction with balloon angioplasty to treat atherosclerosis, the endovascular mechanical implants called stents are commonly used as chronic vascular scaffolds to keep the blood vessel open. Most of commercially available stents are metallic, made of biocompatible alloys such as medical-grade stainless steel and Nitinol, to configure balloon-expandable or self-expanding stents. These stents with mesh-like walls are manufactured by laser micromachining of the specific alloy tubes. The deployment of the self-expanding stents in arteries relies on thermoresponsive actuation of Nitinol [170]. The stent is positioned at the target location via the delivery catheter and then (by removing the covering sheath) allowed to self-expand to its memorized diameter through the martensite-to-austenite phase transformation upon exposure to the body temperature [172, 173]. After their implantation, expanded stents experience elastic recoil of blood vessels, which can lead to their mechanical failures, a continuing issue for these implants. As an approach to address this type of failure, a Nitinol-based actuator called the recoil-resilient ring was investigated to show its ability to improve the radial stiffness of stents when integrated with them [174]. A newer work demonstrated multiple stage expansion of SMA-based stent via wireless RF control aiming to address recoil and restenosis issues of stents [175]. While not as extensive as the case of SMA, the use of SMP has also been investigated in several studies towards self-expanding stent applications. For example, one study presented a synthesized SMP for stent application, reporting that the polymer showed 100% strain recovery [176]. The device displayed high rubbery shear moduli in the range of 2 MPa and the constrained stress-strain recovery cycle showed very low hysteresis. Another work presented a biodegradable and self-expandable SMP stent showing excellent mechanical properties as well as biocompatibility [177].

Thermal therapy commonly known as hyperthermia is a noninvasive technique that has been used to kill cancerous cells [178]. This therapeutic approach was also reported to be effective in suppressing the occurrence of restenosis, the most common post-stenting complication, and following this path, stent-based endohyperthermia was investigated to enable post-stenting thermal stimulation in a wireless manner [179]. This active “hot” stent was designed to electrically resonate when exposed to a RF field and implement frequency-selective heating for vascular treatment. A stent-hyperthermia system based on this principle was demonstrated through animal tests [180, 181]. To circumvent overheating of the stent device under excitation, a biocompatible MEMS circuit breaker chip was developed and integrated with the hot stents (Figure 8a) [182]. This circuit breaker chip functioned as a

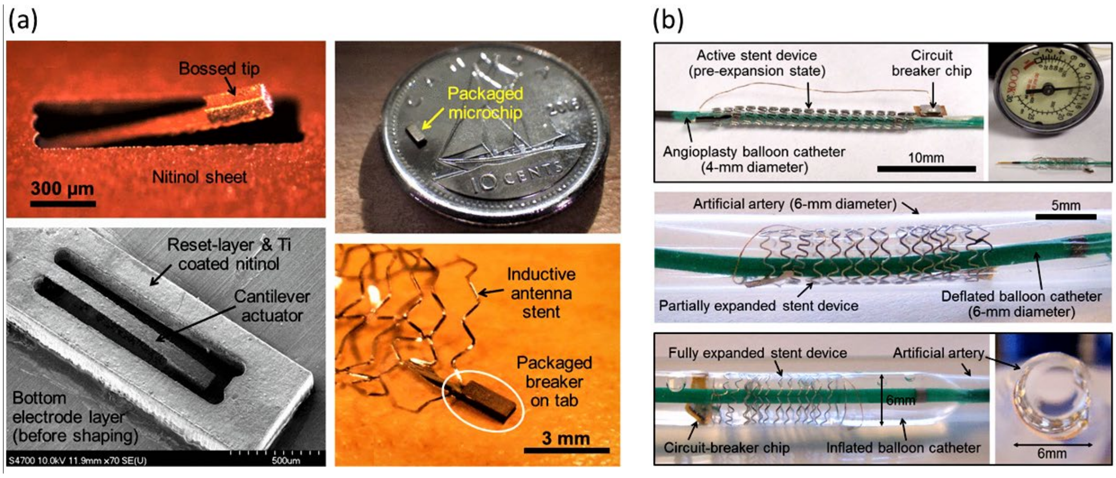

Figure 8. RF-powered resonant "hot" stent for wireless restenosis treatment. (a) MEMS circuit-breaker microchip for self-regulation of stent temperature. Reproduced with permission [182]. Copyright 2017, IEEE. (b) Deployment of the stent device with circuit-breaker microchip. Reproduced with permission [184]. Copyright 2015, IEEE.

thermoresponsive contact switch with a SMA actuator, or an absolute temperature limiter, enabling self-regulation of stent's resonance and thus temperature [182, 183]. Figure 8b shows an expansion process of the integrated stent device demonstrating automatic switching and overheat prevention when wirelessly powered [184]. The reported circuit breaker chip was claimed to be used for temperature regulation of other types of electronic implants.

Aside from stent related applications, shape memory materials have been utilized in other cardiac devices that exploit their actuation and deployment triggered by the body temperature. One example is the SMP-based rings that have been used for cardiac valve repair to reduce mitral regurgitation [185]. Closure devices have been widely used in intervention treatment for congenital heart disease that is known as abnormal anatomy caused by dysplasia. Several studies were reported to develop Nitinol-based closure devices (Figure 9) [186]. This type of devices is delivered into the body using its delivery system in a compressed state and then deployed to its original shape at the target location. A well-known occlude device was realized with two Nitinol woven discs for closure of congenital heart defects [187].

3.4 Surgical and Endoscopic Tools

MEMS actuators offer promising opportunities in creating novel surgical devices as well. In particular, these actuators based on shape-memory materials, piezoelectric, and pneumatic

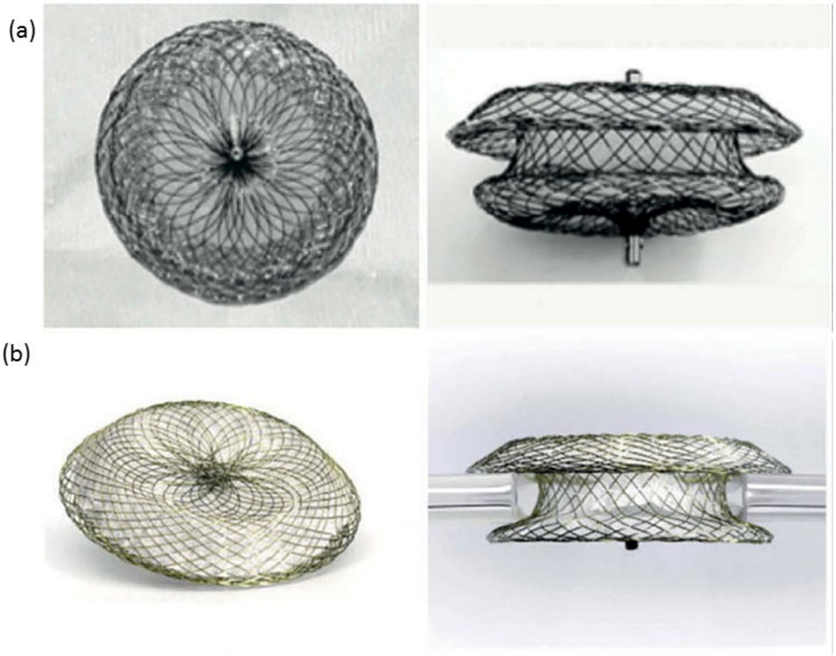

Figure 9. Nitinol-based closure devices for congenital heart disease: (a) Amplatzer ASD Occluder; (b) Occlutech Figulla ASD Occluder. Reproduced with permission [186]. Copyright 2019, Elsevier.

principles and related fabrication processes are paving avenues to miniaturizing and improving the tools for surgical, interventional, and related procedures including catheters, manipulators, endoscopes, and imaging devices. Utilizing the features of nanometer-range resolution and fast response, piezoelectric microactuators have been applied for delivering and scanning high-frequency laser pulses for microsurgery purposes. For example, Ferhanoglu *et al.* reported rapid removal of bulk tumors and bones using the 5-mm-diameter fiber device comprised of an air-core photonic bandgap fiber for delivery of high energy laser pulses, a piezoelectric tube actuator for fiber scanning, and two aspheric lenses for focusing the laser beam [188]. To enhance the visualization of fine biopsy needles under ultrasound imaging, the needle-like catheter that equipped a miniaturized ultrasonic actuator was developed with a PZT layer sandwiched between two flexible electrodes using MEMS technology [189]. Being attached to a catheter, the actuator radiated low-intensity ultrasound for detection of a biopsy needle tip under sonography. Likewise, to perform a non-abdominal operation or microsurgery, a micro ultrasonic scalpel was developed using PZT deposited through a hydrothermal method [190, 191].

Pneumatic actuators shaped with soft and flexible elastomers are considered as one of the most suitable candidates for surgical device applications. Many studies utilized the anisotropic rigidity of PBA in developing bending actuators for active catheter tools. For example, Ruzzu *et al.* reported a system for fixing and orientating the catheter tip consisting of three inflatable microballoons [192]. The microballoons were mounted on the three sides of the catheter tip and controlled by electro-thermo-pneumatic microvalves. When deflated, these balloons exerted a force on the wall of the vessel, causing a change in the position and orientation of the catheter tip. In addition, a telescopic motion was achieved by connecting several PBA pairs in series in order to actuate commercial forceps [193]. Another PBA-based device with a cylindrical microstructure was developed to solve a bubbling problem in the intestinal tract, which caused undesirable stagnation blocking the observation of cells [194]. Supplying air to the artificial intestinal tract via microchannel, the PBA gradually transformed from flat to circular tube that allowed perfusion of the culture media. For endoscopic fluorescence imaging and diagnosis, a flexible end-effector was developed via integration of a PDMS-based PBA, serving as scanning actuator, with an SU-8 optical waveguide using MEMS fabricated techniques [195].

Besides the PBA-based approaches, various efforts have tailored pneumatic and other fluid-driven actuators to develop different surgical tools. For example, a pneumatically actuated micro-gripper was reported to manipulate embryos for cloning applications, (Figure 10a) [196]. The micro-gripper consisted of two main parts; the micro pneumatic chamber with a flexible membrane and the hinged gripper arms connected to the membrane. Supplying pressurized air to the membrane, it deflected both the arms to provide a gripping motion. Traditional laparoscopes used for certain surgical interventions (such as total mesorectal excision) lack a flexibility sufficient to safely maneuver and reach difficult surgical targets. This need was approached through the development of the robotic device composed of two pneumatically actuated identical modules, capable of omnidirectional bending and elongation, to allow for highly dexterous and safe navigation [197, 198]. Becker *et al.* developed a tissue retraction device for treatment of lesions in the gastrointestinal tract [199]. This device was comprised of three main integrated components, i.e., a rigid expandable geometric structure, inflatable pneumatic actuators, and a vacuum gripper fabricated using the pop-up book MEMS technique. Similarly, to improve the distal dexterity and enable tissue retraction, the soft pop-up actuators were exploited to form a multi-articulated robotic arm (Figure 10b) [200]. Here, the millimeter-scale hybrid soft pop-up actuators were embedded with capacitive sensing elements to achieve proprioceptive actuation. Endoscopic devices also often suffer from limited distal tip dexterity, and this issue has been tacked by

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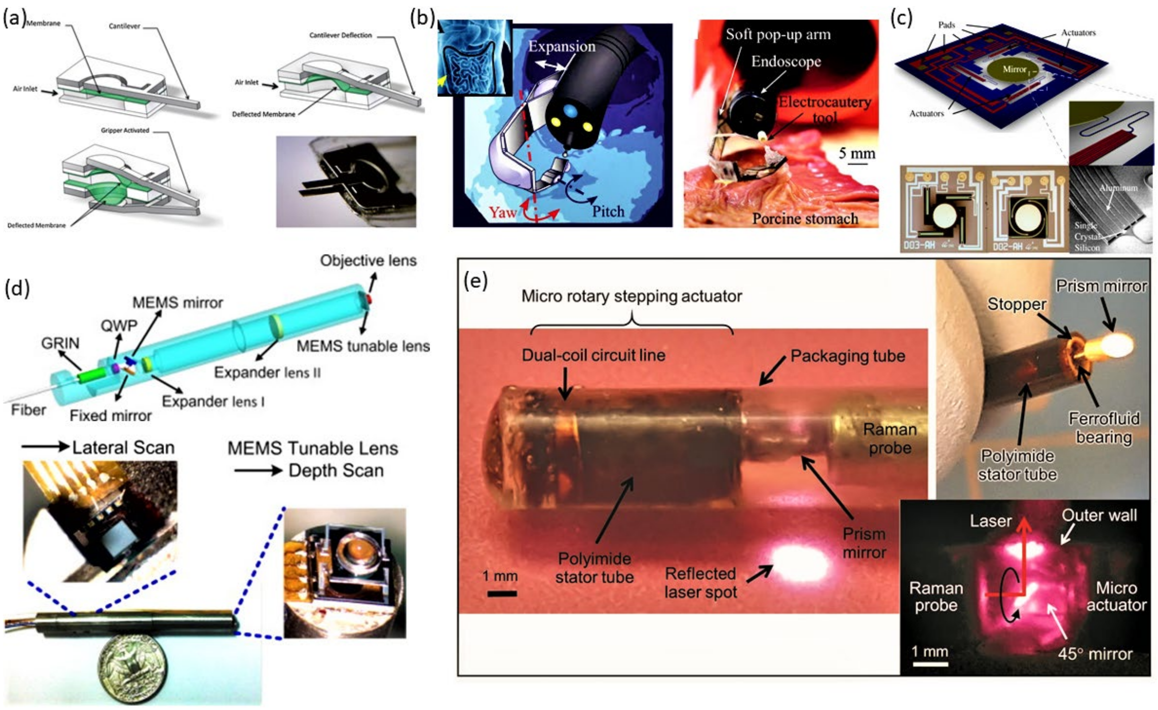

Figure 10. MEMS-enabled surgical and endoscopic tools. (a) Pneumatically actuated micro-gripper. Reproduced with permission [196]. Copyright 2015, Elsevier. (b) Conceptual 3D model and optical image of the soft pop-up actuator. Reproduced with permission [200]. Copyright 2014, Elsevier. (c) Electrothermally actuated MEMS scanning mirror for OCT probe and optical images of fabricated micromirrors. Reproduced with permission [205]. Copyright 2008, IOP Publishing. (d) MEMS-based 3D confocal scanning microendoscope. Reproduced with permission [207]. Copyright 2013, Elsevier. (e) Side-viewing Raman probe with integrated MEMS rotary motor. Reproduced with permission [208]. Copyright 2019, Wiley-VCH.

incorporating pneumatic actuation mechanisms with them. For example, pneumatic tubular actuators were developed and optimized for applications in flexible microactuator-based endoscopes to facilitate colonoscopy [201, 202] as well as a bronchoscope to observe lung airway and obstructions in the bronchus [203]. Combining a chip-on-tip CMOS camera with an elastic inflatable microactuator, Gorissen *et al.* presented a flexible endoscope for navigating through intricate topologies of the human body [204].

The endoscopic devices with active scanning functions have been developed by adopting different actuation methods besides pneumatic one. For example, to obtain *in-vivo* local images for tissue diagnostics, an active optical coherence tomography (OCT) probe was developed with two-axis scanning electrothermal MEMS micromirror, gradient refractive

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index lens, and single-mode fiber integrated on silicon optical bench (SiOB) substrate (Figure 10c) [205]. For three-dimensional (3D) imaging, a 2-axis MEMS mirror with a preset (45°) angle was directly integrated on a SiOB. The probe was enclosed within a biocompatible, transparent and waterproof polycarbonate tube for *in-vivo* applications. A similar active OCT probe enabled by an electrothermal MEMS mirror was also reported for real-time imaging of internal organs such as gastrointestinal tract, stomach, small intestine, and esophagus [206]. The unique features of this MEMS-mirror design were a large scan range of ±30°, a high speed of about 2.5 frames per second, and a body-safe driving voltage of 5.5 V. Following the same scanning approach, a fiber-optic 3D microendoscope with a confocal scanning function was developed for early cancer diagnosis (Figure 10d) [207]. The probe was comprised of electrothermal MEMS scanning mirrors that offered a large imaging field via both lateral and axial scans with low driving voltages. For endoscopic probes, full circumferential scanning around the probe is an important ability for screening and detecting lesions on the walls of luminal organs without blind spots; however, this need is difficult to meet with 2D MEMS scanners. A tubular MEMS rotary motor was developed for this application segment and enabled a side-viewing Raman spectroscopy (RS) probe (Figure 10e) [208-210]. This electromagnetic MEMS motor, developed using a self-sustained ferrofluid bearing in the catheter tube, provided both stepping and continuous rotations of a probing laser beam and demonstrated full 360° tissue imaging/analysis via RS [208] as well as OCT [210] modalities *ex vivo* and *in vivo*. The motor was also engineered to provide hydraulic axial motion in addition to rotation for 3D luminal imaging without requiring an external probe positioning system [209].

4. Conclusion

Continuous advancement of microactuator technologies, along with their fabrications and integration methods, has led to the emerging areas of biomedical microsystems including smart implants and surgical devices in miniaturized forms. The success in a targeted application critically relies on the appropriate selection of a particular actuator, which depends on various factors besides the fundamental performance of the actuator itself, including powering and control methods, biocompatibility, level of required packaging, and cost effectiveness. With an aim to facilitate the development of this emerging field while addressing those key factors, this paper has presented a comprehensive review of the MEMS actuators investigated for their biomedical uses with a focus on several common transduction

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types. Table 1 presented a clear comparison of these actuation techniques and their characteristics. The use of thermoresponsive materials is a promising route to enabling smart actuation functions with simple designs, an advantageous feature towards device miniaturization. Among them, SMA offers large displacement and force whereas SMP possesses relatively high recoverable strain levels. The PNIPAM hydrogel can be compatible with the standard photo-patterning process and allows for adjustment of its temperature threshold. The above attributes often make them suitable for applications in drug delivery, cardiac and surgical devices. The electromagnetic actuators with their large displacement, fast response and low-voltage powering features are usable for the development of LoC and their active elements such as micropumps and microvalves. The piezoelectric actuators are a powerful enabling technology for devices targeted at micro/nano-scale positioning, micropumps, and micro-robotics. Being softer and flexible, the fluid-driven actuators offer a variety of application opportunities in surgical devices.

Exploiting these favorable features, thermoresponsive, electromagnetic, and piezoelectric actuators are widely applied for implantable devices. However, they require an attention in a few factors. For their medical and implant applications, these actuators are often powered using batteries. This may cause not only the need for periodic replacement through surgical procedure but also significantly increase the overall device sizes and hence their invasiveness in the body. While wireless powering and control methods for smart implants are being widely explored, the issues around their efficiency, reliability, and biocompatibility/safety will need to be addressed. The safety factor includes proper heat management and necessary packaging that, in turn, can negatively impact on the device performance and size. One of the key approaches to addressing powering issues would be *in-situ* energy harvesting from the implanted environment, which may be achieved using similar principles of some of the abovementioned MEMS actuators but with reversed transductions converting environmental stimuli to electrical energy.

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Types		Working principle	Advantages	Disadvantages	Energy density (J/m^3)	Efficiency (%)	MEMS Applications
Thermoresponsive actuators	SMA	Shape-memory effect	• Large displacement • Large force • High mechanical robustness • Corrosion-resistant	• Slow temporal response • High power consumption	~10^7 [211]	<10 [212, 213]	Surgical tools [22, 68] Implantable devices [65] Microgrippers [60, 67] Micropumps [60, 63, 70]
	SMP	Shape-memory effect	• Structural flexibility • Large strains • Low density • Tunable transition temperature • Biodegradable properties	• Slow temporal response • Low recovery stress	$2\text{-}6\times10^5$ [214]	<10 [213]	Endovascular devices [74, 75, 176, 177, 185] Drug delivery devices [74, 166, 167]
	Temperature-Sensitive Hydrogels	Phase transition	• Tunable degradation features • Tunable mechanical features • UV-sensitive	• Slow temporal response	3.5×10^5 [211]	1.32 [215]	Surgical tools [85] Microvalves [153-157] Drug delivery [84, 86, 88-90, 151, 153]
Electromagnetic actuator		Magnetization effect	• Simple drive mode • No nonlinear effect • High field energy density • Fast response • Large deflection at low input voltage	• High power dissipation for driving coils • Volumetric scaling of produced electromagnetic forces that rapidly drop as the device size shrinks	4×10^6 [213]	>90 [212, 213]	Microgrippers [100] Micropumps [101-103]

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			• Parasitic loss at high frequency			Microvalves [104]
Piezoelectric actuator	Piezoelectric effect	• Fast response • High displacement resolution • High efficiency • Compact structure • Immunity to magnetic field	• Require high-temperature thermal processes for incorporation of piezo materials • High driving voltage • Large hysteresis nonlinearity	10^5 [213]	>90 [212, 213]	Micropumps [114, 115] Micro-robotics [116]
Fluid-Driven actuator	Elastic deformation	• High flexibility • Large displacement • Lightweight • High power-to-weight ratio • Simple/low-cost fabrication	• Low force exertion • Limited number of degree of freedom	1.2×10^6 [216]	30-40 [212, 213]	Medical and surgical devices [136, 137]

Table 1. Performance comparison of actuation techniques

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