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4D printing soft robotics for biomedical applications

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ABSTRACT

Soft robotics has grown rapidly as an attractive manufacturing technique at micro/nanoscales, especially in the field of biomedical engineering, due to its mobility and compact size. As an emerging additive manufacturing technique, four-dimensional (4D) printing can replicate natural physio-mechanical changes over time leading the transition from static to dynamic. As such, 4D printing is widely investigated and applied in fields ranging from mechanical engineering and material science, to biomedical engineering. By combining the unique ability of 4D printing to create dynamic morphological changes under certain stimuli and biocompatible soft material based micro-/nanorobots, a new promising platform with precise controllability and unlimited reversible actuation is expected to enhance the role of 4D printing for biomedical applications. In this review, we systematically introduce soft robots and further summarize current 4D printing approaches to fabricate soft robots. Moreover, a broad scope of potential applications of 4D soft robots in biomedical engineering is exclusively discussed. We finally conclude with current challenges and limitations, as well as future directions, for 4D printing soft robot technology.

1. Introduction

Robotics is defined as the "intelligent connection between perception and action" [1]. While this has historically translated to programmable robots delivering locomotive functions, the focus of robotics is expanding greatly across nearly unlimited research fields, increasing its application base. An emerging application in the field of robotics is the development of soft robotics [2,3]. Soft robotics is a rapidly growing field attracting investigators with interests ranging from robotics and mechanical engineering, to biomedical engineering. Whereas conventional mechanical robots for industrial use traditionally integrate technology at the macro scale, soft robots utilize advanced integrated technology of intelligent materials, control systems, chemistry, and acoustics at micro/nano scales [4]. The study of soft robotics is based on an understanding of soft materials. In contrast to stiff materials that are utilized for the design of conventional mechanical robots, soft materials primarily contribute to applications targeting the composition of the natural world. For instance, animals comprised of a bony framework, such as mammals and primates, including humans, fundamentally consist of soft materials as well, and in greater proportion [5,6]. According to Kim et al., skeletal muscle is responsible for 42 % of body mass, while the skeleton itself only accounts for 11 % [5]. Moreover, due to their deformability and flexibility, soft materials have become essential components for soft robotics, emerging as promising platforms with a great capacity for complex design and precise controllability in biomedical applications including smart drug or cell delivery, microsurgery devices, and *in vivo* actuation for biosensing [7].

Four-dimensional (4D) printing was first revealed in 2013, approximately 30 years after three-dimensional (3D) printing was patented, and has attracted a great deal of research interest in the last 5 years [7–10]. The most common form of 4D printing involves shape transformation under exposure to stimuli, such as ultraviolet light, heat, or other energy sources [7]. In addition to one-way change, another characteristic of most 4D printing is reversibility [7]. In order for a 4D printed structure to be properly stimuli-responsive and reversible, an appropriate selection of stimuli-responsive materials is critically significant. The stimuli-responsive materials used in 4D printing can be divided into external and internal triggers. The external triggers are

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often magnetic fields, acoustic waves, light, and electric fields, whereas controllable or voluntary chemical reaction is classified as an internal stimuli-responsive system [11].

Upon merging the advancing technologies of soft robotics and 4D printing, a wide range of applications are emerging in the fields of biomedical engineering, material science, and mechanical engineering. Even though a number of soft robots have been still fabricated using classical manufacturing systems, which costs excessive energy consumption and unnecessary waste of materials, the claim for new techniques in soft robotics has been continuously arisen [12,13]. Regarding that, 4D printing can be considered significantly advantageous for the fabrication of soft robots compared to other techniques. 4D printing primarily stems from 3D printing so that it provides technical advancements including freedom in modeling new 3D structured soft robots, besides the main strengths of 3D printing; controllability, repeatability, and reproducibility [6]. Also, in this review, we focus on background principles and techniques that account for the fabrication of 4D printing incorporated soft robots with applications. Research on soft robotics supports the feasibility and potential to adapt 4D printing techniques as an alternative fabrication method. We will discuss both soft robotics and 4D printing, and make suggestions for future direction for 4D soft robotics to be further improved and integrated, expanding the scope of biomedical applications.

2. Technical approaches for 4D printing

The term, 4D printing was originally defined as a process that enables material transformation over time, or a material system that changes from one shape to another [14]. In other words, 4D printing was known as a combined concept blending 3D printing with structural changes, such as shape, physical property, or functionality over time [14–19]. As more relevant studies have been performed, the definition of 4D printing has evolved toward self-assembly, self-adaptation, and self-repair [15]. In order to obtain a 4D printed construct, expertise in 3D printing is required, as well as knowledge of and access to the following: 1) stimulus to trigger changes in shape, properties, or functionality, 2) facility to initiate 3D printing, 3) theoretical model to predict physical or chemical behavior of materials, and 4) stimuli-responsive material (SRM) integration [11,15]. Among them, SRM is considered the most critical component and is further classified into multiple types of shape memory materials (SMMs), which will be discussed in a corresponding section.

Another important aspect of 4D printing is its technical approach. As 4D printing is the integration of time and 3D printing, the technique fundamentally stems from conventional 3D printing approaches. For instance, a light source, such as a UV light or a laser beam can be utilized to promote photo-polymerization, where each technique is known as digital light processing (DLP) and stereolithography apparatus (SLA), respectively [20]. SLA is one of the commonly used printing techniques due to its precise resolution control, which is led by a small scale laser tip [6]. In contrast, DLP has recently gained attention from many researchers as it holds rapid printability by employing an optical mirror to generate desired patterns [20,21]. In addition to the light assisted systems, the most widely used printing platform is fused deposition modeling (FDM), which is also known as fused filament fabrication (FFF). This approach incorporates the state transition of printing materials by applying sufficient heat [6,8]. Although FDM possesses outstanding versatility and offers an extensive selection of thermoplastic materials, the availability of the system for 4D printing is questionable due to the limited compatibility with SRMs.

Based on its numerous advantages, such as energy source-specific transformation and volume reduction, 4D printing has risen as a promising technique for biomedical applications. Numerous representative studies conducted by the researchers from Zhang's lab at the George Washington University (GWU) begin to investigate such applications with a strong focus on biocompatible material selection. Recently, a novel near-infrared light (NIR) responsive 4D nanocomposite was developed that consisted of thermally responsive SMM and photothermally responsive graphene obtaining a dynamically controllable 4D printing platform with the incorporation of a biologically harmless energy source [10]. Fig. 1 shows the gradual transformation of the 4D printed nanocomposite models under NIR exposure. In addition, another recently reported study demonstrated the fabrication of a biomimetic, 4D dynamic shape-changing, tissue scaffold [22]. An environmentally friendly smart natural lipid, soybean oil epoxidized acrylate, was used as an ink in a photolithographic-stereolithographic-tandem approach for the cardiomyogenic differentiation of stem cells. As shown in Fig. 2, the 4D printed, temperature-sensitive constructs sequentially transformed over time. More specifically, Fig. 2**a** illustrates a reversible 4D heart-shaped structure that possesses potential for minimally invasive surgery. Additionally, a stereolithographic printing technique was used to create a series of internal, stress-induced, 4D printed constructs **(**Fig. 3**a-c)** [23]. In this work, the researchers demonstrated the current advancement of the 4D printing technique with its outstanding potential for use in biomedical engineering. A naturally-derived photocrosslinkable monomer was utilized to fabricate a reversible 4D transformation system. Based on this novel approach, 4D reprogrammable nerve guidance conduit for peripheral nerve injury repair was demonstrated **(**Fig. 3**d-f)**. In addition, the amount of graphene-based nanoparticle contributed to the serial flying motion of a 4D printed bird **(**Fig. 3g**)**.

Micro- or nanoscale robots are primarily designed for swimming throughout the entire human body to convey their biomedical functionalities. As such, an adequate power supply is necessary to generate locomotion. The biggest challenge is managing how to provide acceptable conditions for the actuation of soft robots. This challenge can be further divided into two approaches. First, soft robots must be aware of their surroundings and obtain energy for propulsion [24]. Then, they must possess adaptability in the application environment [24]. Another consideration for locomotion in the sub-microscale exists in the low Reynolds number environment, where viscous forces are dominant over inertial forces [4]. Due to the limitation of space, conventional power supplies for machines, such as batteries or macroscale power generators, are unable to be adopted toward soft robotics systems. Therefore, material-specific design strategies are essential to generate locomotion of soft robots at the sub-micro scale.

The majority of these small swimmers are propelled by external stimuli. The external power sources to create locomotion of soft robots include magnetic fields, acoustic waves, light, temperature, and electric fields **(**Fig. 4**)** [24–30]. One of the noticeable concepts for external stimuli based propulsion of small swimmers is the transition from the symmetric to the asymmetric system [27]. Most of the reported studies that demonstrate microscale propulsion using external stimuli focus on how to break the stability of the system to generate locomotion. In that regard, the key to magnetic actuation is the permanent or ephemeral magnetization of soft robots. Depending on the type of magnetic robots in microscale, and applied actuation methods, soft robots exhibit multiple swimming mechanisms [24,27,25–30], which possess the potential to be used for the fabrication of 4D soft robots to perform biomedical tasks in the prospective studies. Thus, such propulsion systems can be employed as external stimuli to trigger and control motions of 4D soft robots. For example, functionalized silicon dioxide (SiO_2) based propellers with depositing a very thin layer of a ferromagnetic material in nanoscale can be instantaneously driven by a uniform magnetic field [31]. Also, adequate use of ephemeral magnetic stimulation with environment-specific structure, such as bacteria flagella inspired design for small swimmers in a low Reynolds number fluid can further enhance their propelling ability [32]. In addition, the utilization of acoustic waves is an alternative candidate to drive micromotors in fluids, as observed with high-frequency acoustic waves (MHz-scale) inducing propulsion of rigid particles [33,34]. Lui et al. developed a plasmonic motor that employs a light-induced torque, which is primarily from

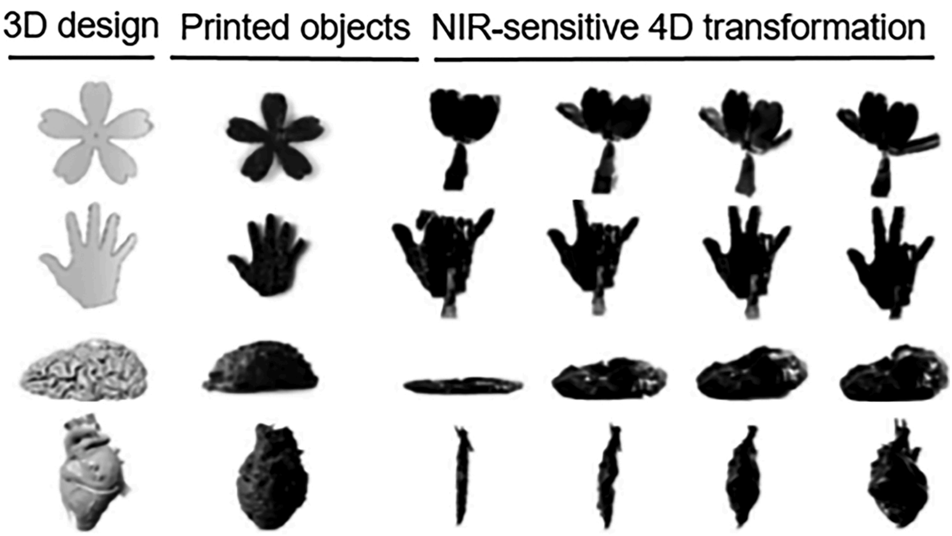

Fig. 1. 4D transformation process of light-sensitive constructs, such as a blooming flower, human hand gesture, and dilated brain and heart. The dynamic control of the 4D transformation behavior could be obtained under NIR exposure. Image adapted from [10] with permission.

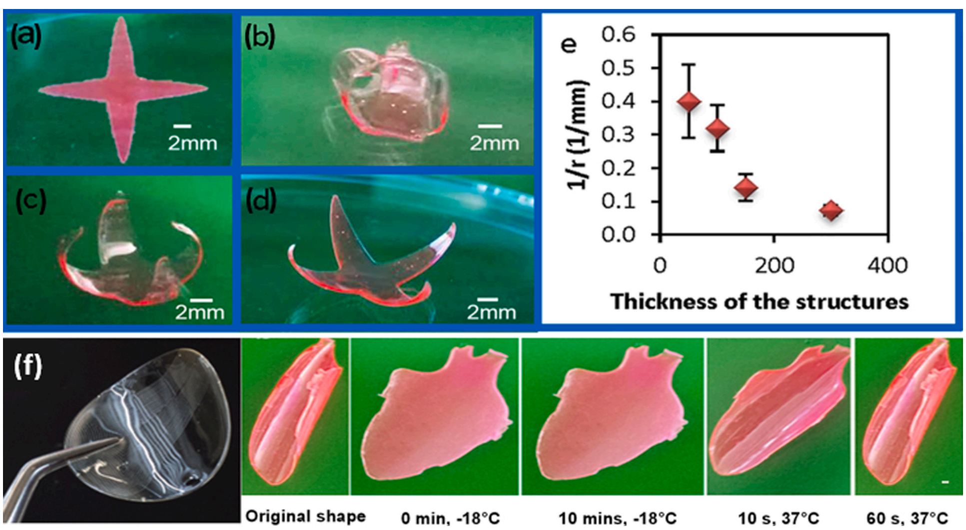

Fig. 2. A dynamic, 4D printed structure shape-changing process. (a)-(d) The shape transformation of a star-shaped construct after being exposed to external stimulation. The thickness of the structure increased from 100 μm (b) to 150 μm (c) and 300 μm (d). (e) The thickness vs. curvature. (f) Photo images of a heart-shaped construct after 4D printing and its dynamic transformation under temperature variance over time. The stretched heart-shape structure gradually recovered its original shape at 37 °C. Scale bar, 2 mm. Images adapted from [22] with permission.

electron inertia [35]. In their study, a linearly polarized Gaussian beam with wavelength control generates a different amount of torque, which results in various rotational speeds. Similarly, the electric field driven locomotion is also desirable. Loget et al. generated a linear and rotational motion of conducting objects using a bipolar electrochemical approach [27]. Their approach relies on the polarization of a conducting object to promote chemical reactions, which selectively generate gas bubbles to propel the system.

While there are multiple external sources for soft robotic propulsion systems, the internal propulsion mechanism most likely relies on one fundamental source, a chemically powered motor (Fig. 5**a**, **b**). The chemical biomotor can be further divided into bubble and diffusion-based propulsion systems. Bubble-based propulsion is one of the most omnipresent internal propulsion mechanisms. The bubble propulsion mechanism is primarily based on the conversion of chemical energy obtained from a surrounding environment, or chemical decomposition of the motor into kinetic energy to generate locomotion (Fig. 5**c**) [36, 37]. For example, the movement created by catalytic decomposition of hydrogen peroxide (H_2O_2) into O_2 bubbles was reported to drive a tubular microjet up to 720 nm ms^{-1} in a low Reynolds number environment, which is appropriate for delivery vehicles in biological systems [36]. The next phase of the microscale propulsion mechanism is diffusion based self-propelling, which is specifically referred to as diffusiophoresis propulsion. In order to create autonomous movements of a microswimmer, diffusion-based propulsion mainly utilizes an uneven accumulation of reaction product particles. In other words, excessive accumulation of decomposition materials promotes the product to diffuse away, which ultimately results in the propulsion of the small swimmer [37–39]. As described in Fig. 5**d**, **e**, the enzymatic site and reactive particles in an imbalanced environment contribute to an asymmetric distribution of reaction particles [39]. As the accumulated reaction particles fade away by diffusion from high to low concentration areas to preserve the equilibrium, the microswimmer is continuously propelled along the concentration gradient.

3. Material selection for 4D printing Soft robotics

3.1. 3D printing shape memory materials

In the context of engineering actuators, 4D printed soft robots begin with a proper selection of materials. By incorporating SMMs, the transition from 3D to 4D printing occurs with the integration of biorobotics.

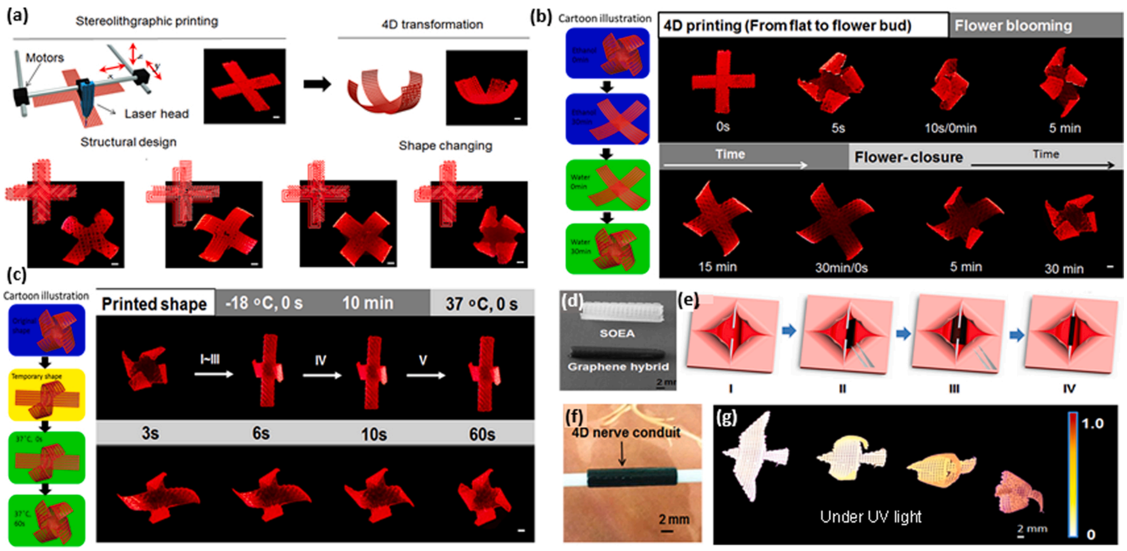

Fig. 3. (a) A schematic illustration of the stereolithographic 3D printing and the 4D shape transformation processes. Multiple types of claw-like actuation were achieved by different pattern designs after stress relaxation (Bottom). Scale bar, 2 mm. (b) A schematic illustration (left) and photo images (right) of the reversible 4D transformation by a series of internal stresses over time. Flower blooming and closure were initiated and controlled as the printed construct was immersed in ethanol and water, respectively. Scale bar, 2 mm. (c) A schematic illustration and demonstration of the shape memory process with the 4D printed flower architecture. Scale bar, 2 mm. (d) A photo image of fabricated 4D reprogrammable nerve guidance conduit for peripheral nerve injury repair. The white conduit (top) does not contain graphene, whereas the black (bottom) one consists of 0.8 % graphene. The dimension of the printed construct was 0.8 × 1.5 cm in a rectangular shape, then a conduit was obtained via an interior stress-induced 4D transformation. (e) A schematic illustration of the 4D nerve conduit entubulation. (f) The integration of the 4D nerve conduit with the two stumps of a defect model. (g) A series of fabricated flying birds with various graphene contents from 0 to 0.8 %. Additional graphene resulted in enhancing 4D curvature. Images adapted from [23] with permission.

SMMs are critically essential components for this approach due to their unique abilities, such as restoration of their original shape or one-way deformation in response to certain internal or external triggers [11,40,41]. SMMs possess the ability to memorize and restore their programmed shape under certain stimuli [42]. Theoretically, internal and external triggers to promote plastic deformation of SMMs can be physical, chemical, or a mixture of multiple stimuli. Among them, temperature-sensitive SMMs have been most widely used in a majority of the relevant research due to the variety of SMM selection. Categorically, SMMs are classified into shape memory alloys (SMAs), shape memory polymers (SMPs), shape memory composites (SMCs), and shape memory hybrids (SMHs) [40,43]. Among a variety of invented SMMs, SMPs have been most widely utilized for biomedical applications due to their biocompatibility, biodegradability, strength:weight ratio, and recoverable strain [40,44–46]. The fabrication steps that utilize SMPs for 4D soft robotics usually incorporate thermomechanical programming processes after printing [20]. With regard to reversible thermomechanical programming (RTP), intermediate melting temperature for partial melting is required during the actuation [47]. In this state, the thermodynamically preferred configuration of the polymer network can be achieved by melting and dismantling the original crystalline scaffold structure [48]. The intermediate melting temperature and crosslink density of SMPs account for the degree of reversibility. Therefore, the state transition control from metastable and melting states to recrystallization is the key for RTP [48].

For example, Jin et al. recently performed a thermal- and photo-reversible bond incorporated programming technique to fabricate crystalline SMP based soft robots [49]. These processes enabled photo-induced dimerization and spatially reversible actuation to fabricate soft robots in 3D. Liu et al. demonstrated that magnetic fields can be used to program temporary shapes of photothermal-responsive SMPs, in which magnetic microparticles were embedded into thin films [50]. In their study, the reconfiguration of the SMP was determined by external photo-thermal heating, and simultaneous actuation was controlled by the magnetic field (Fig. 6a). In addition, biocompatible porous scaffolds with soybean oil epoxidized acrylate were 4D printed with SLA by researchers from Zhang's lab at the GWU [51]. The printed temperature-sensitive scaffolds presented reversible deformation and recovery of their original shape at human body temperature. Also, 4D printed architectures using temperature-sensitive composite materials were demonstrated in a similar manner (Fig. 6**b**) [52]. Based on the properties of SMPs, they possess the ability to perform rapid soft robotic actuation for use internally and externally with the human body. However, the miniaturization and the development of shape transition temperature, such as the normal human body temperature, are still questionable.

While the aforementioned SMPs exhibit the temperature-responsive effect, some portions of the SMAs are known to exhibit the temperature memory system [40]. Also, SMAs have acceptable biocompatibility for biomedical engineering applications. For example, Ti-based SMAs including Ti-Ni, Ti-Nb-Al, Ti-Nb-Sn, and others have historically been a solid platform for orthodontic arch-wires, orthopedic implants, and stents due to their superelastic effect [53]. High performance, biocompatible SMAs are capable of reversible, and cyclic, robotic functions such as bending and anchoring motions. However some prominent SMAs, such as those that are Al- and Ni-based, lack biocompatibility.

Another basic form of SMMs involves combining multiple SMMs to create a responsive system to a certain stimulus. For instance, in the work done by Huang et al., a cylindrical spring was fabricated with the combination of an SMH and an SMA [40]. The elongation and shrinkage of the fabricated spring were completely controlled by external temperature (Fig. 7a). Nanoparticle-incorporated polymeric hydrogels also can be an example of multi stimuli-responsive SMMs such as those with thermoresponsive magnetic platforms [54].

3.2. Combination of smart and conventional materials

As addressed by de Marco et al., 2D printing of combined conventional and smart materials is one of the strategies to derive anisotropic stresses [41]. In this perspective, there are many approaches for the dimensional transformation of 2D/ 3D polymer sheets to 3D/ 4D constructs including conventional lithographic methods, sputtering and

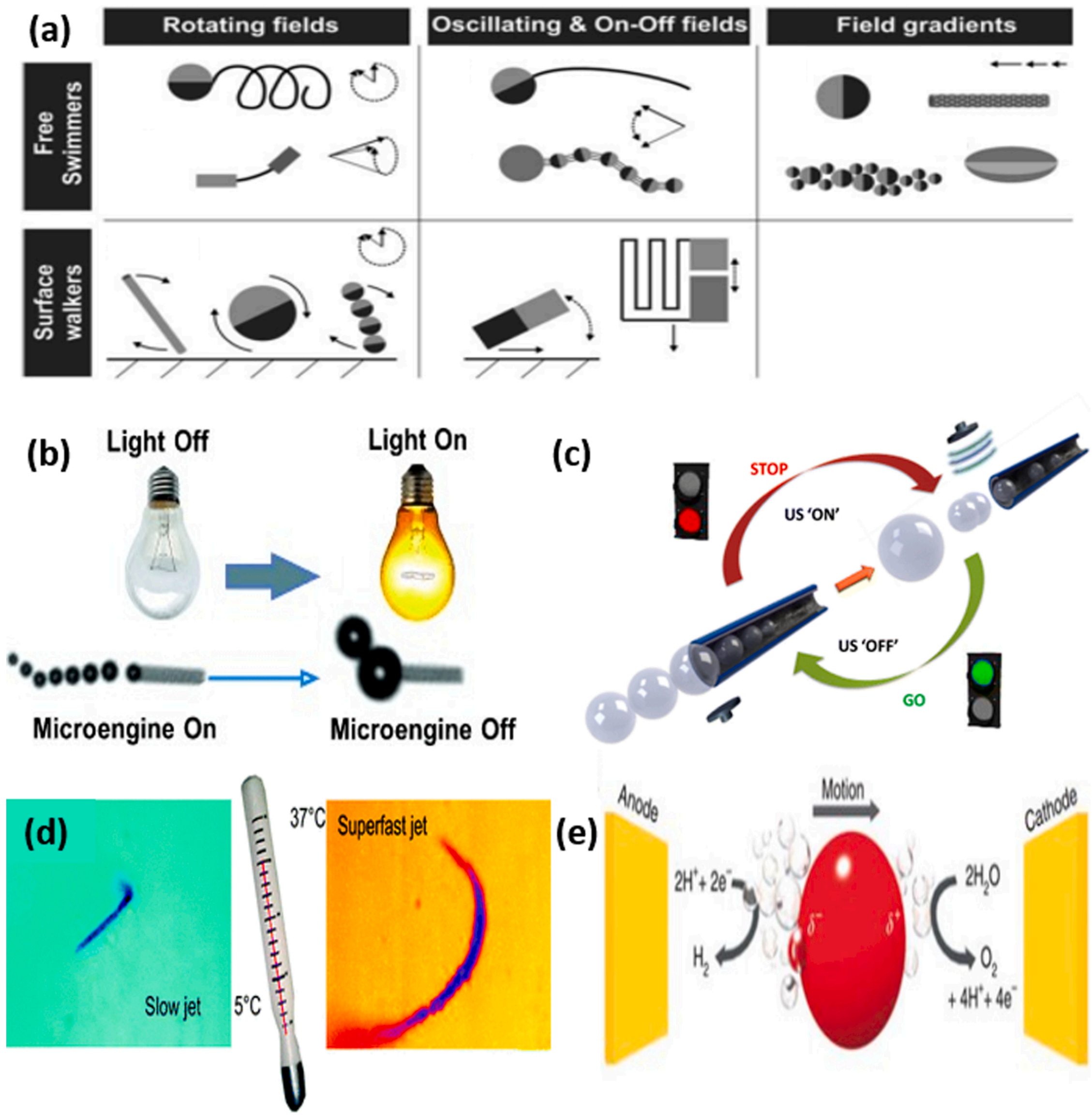

Fig. 4. Schematic images of miscoscale propulsion systems using external power sources. (a) Types of magnetic microrobots and their actuation methods. Image adapted from [24] with permission. (b) Light-induced microscale propulsion. Image adapted from [29] with permission. (c) Acoustically triggered miscroscale propulsion. Image adapted from [28] with permission. (d) Thermally triggered miscroscale propulsion. Image adapted from [30] with permission. (e) Miscroscale propulsion triggered by bipolar electrochemistry. Image adapted from [27] with permission.

evaporation, and others to induce bending, folding, or wrinkling [55]. One of the most important factors that must be taken into consideration for this approach is the compatibility with the 3D printing technique. In that sense, the PolyJet 3D printing system, which utilizes a direct material jetting of droplets and subsequent photo-polymerization under UV lights, has been widely utilized for the fabrication of components with smart and conventional materials [56–58]. Likewise, the proper selection of printing materials is significant in this approach. The combination of a non-smart material with SMPs is generally considered suitable due to their remarkable advantages for use in this regime. A capability of convoluted shape transformation and repeatable programmability of initial and final shapes, based on wide availability and tolerability of SMPs is one example of this combination [47].

Ge et al. created a more complex 4D printed shape memory structure in high resolution by utilizing microscale SLA with multiple SMPs (Fig. 7**b)** [59]. By blending a photopolymerizable hydrogel and SMPs at different ratios, they obtained an ideal glass transition temperature for the printed architecture. As a result, the recovery ratio could be a function of only temperature over time with the reversible bent structure restoring its original shape as the temperature gradually reached the glass transition temperature. Another method that utilizes thermomechanical properties of the hyperelastic polymer layer and geometrical modification of SMP has also been performed [60]. In their approach, thin bi-layered strips with a hyperelastic polymer and an SMP could be programmed and transformed into multiple different shapes due to their inherent response systems to thermomechanical changes. In the study performed by Wang et al., soft robots with locally programmable actuation to sense and respond to environmental modification were demonstrated [61]. The work involved the combination of multiple polyimide films, liquid crystal elastomers with carbon black nanoparticles (LCE-CB), and innervated heater-based bimorphs into a soft robotic construct for thermomechanical programming to generate crawling locomotion. The mismatch of thermal conductivity between the upper layer of Kepaton film, and the bottom layer of LCE-CB resulted in deformation upon thermal stimulation. By modifying the number of innervated heaters, allocation, and order of activation, various complex shape programming was achieved in this study [61]. The representative studies mentioned above are summarized in Table. 1.

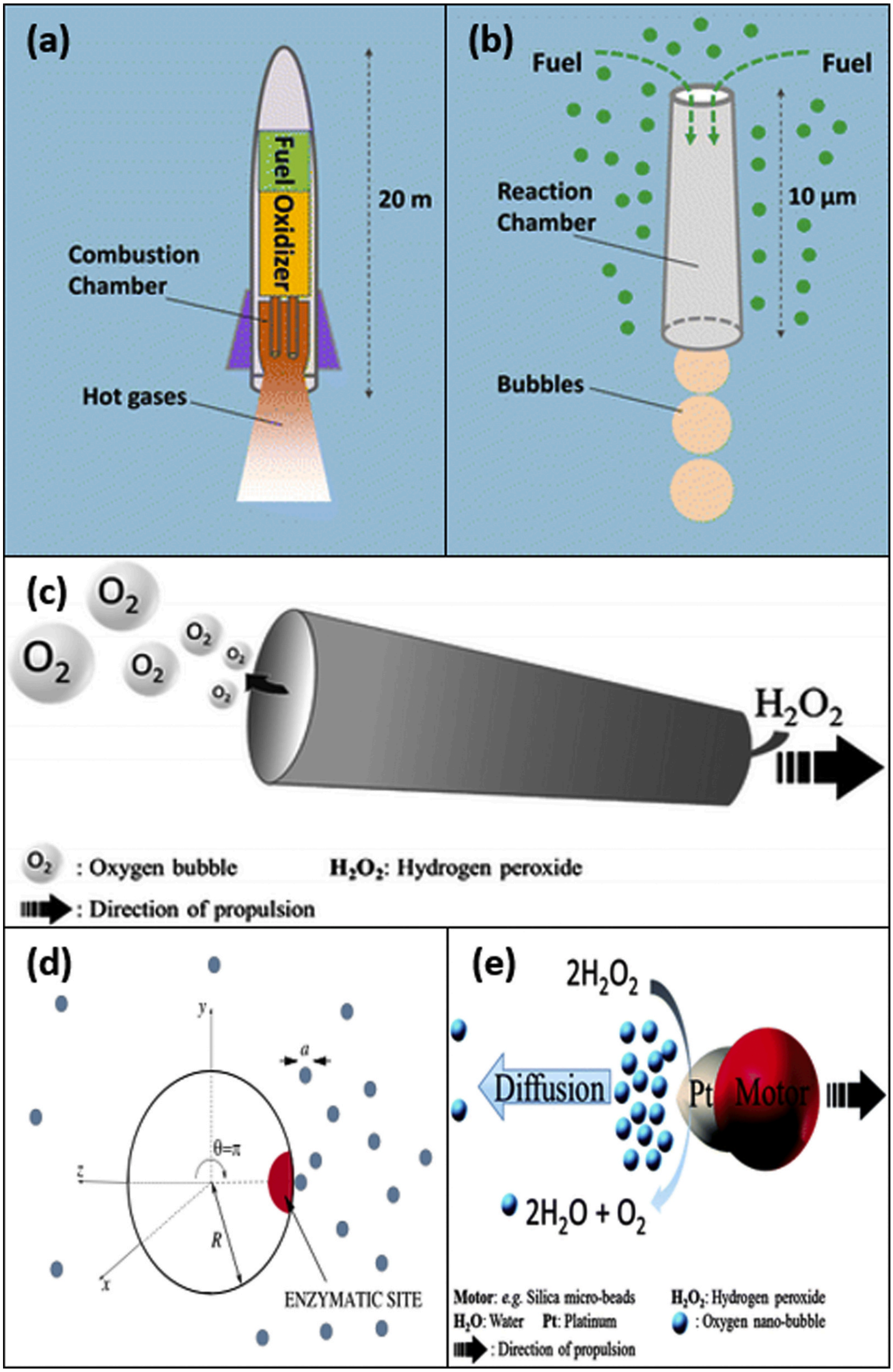

Fig. 5. Schematic images of microscale propulsion systems using an internal power source (chemical). Comparison of conventional macroscale thrust system based on chemical fuels (a) vs microscale (b). Images adapted from [25] with permission. (c) An example of a micro/nanomotor under the bubble propulsion mechanism. The released oxygen bubble and a Pt catalyst on the inner surface generate the propulsion by the peroxide decomposition. Image adapted from [37] with permission. (d) Schematic representation of the diffusiophoresis model. The unevenly concentrated gradient of reaction products generates the propulsion mechanism to move the sphere. Image adapted from [39] with permission. (e) Another schematic representation of the diffusiophoresis model. As the propulsion mechanism is generated by diffusiophoresis, the motor moves against the catalyst. Image adapted from [37] with permission.

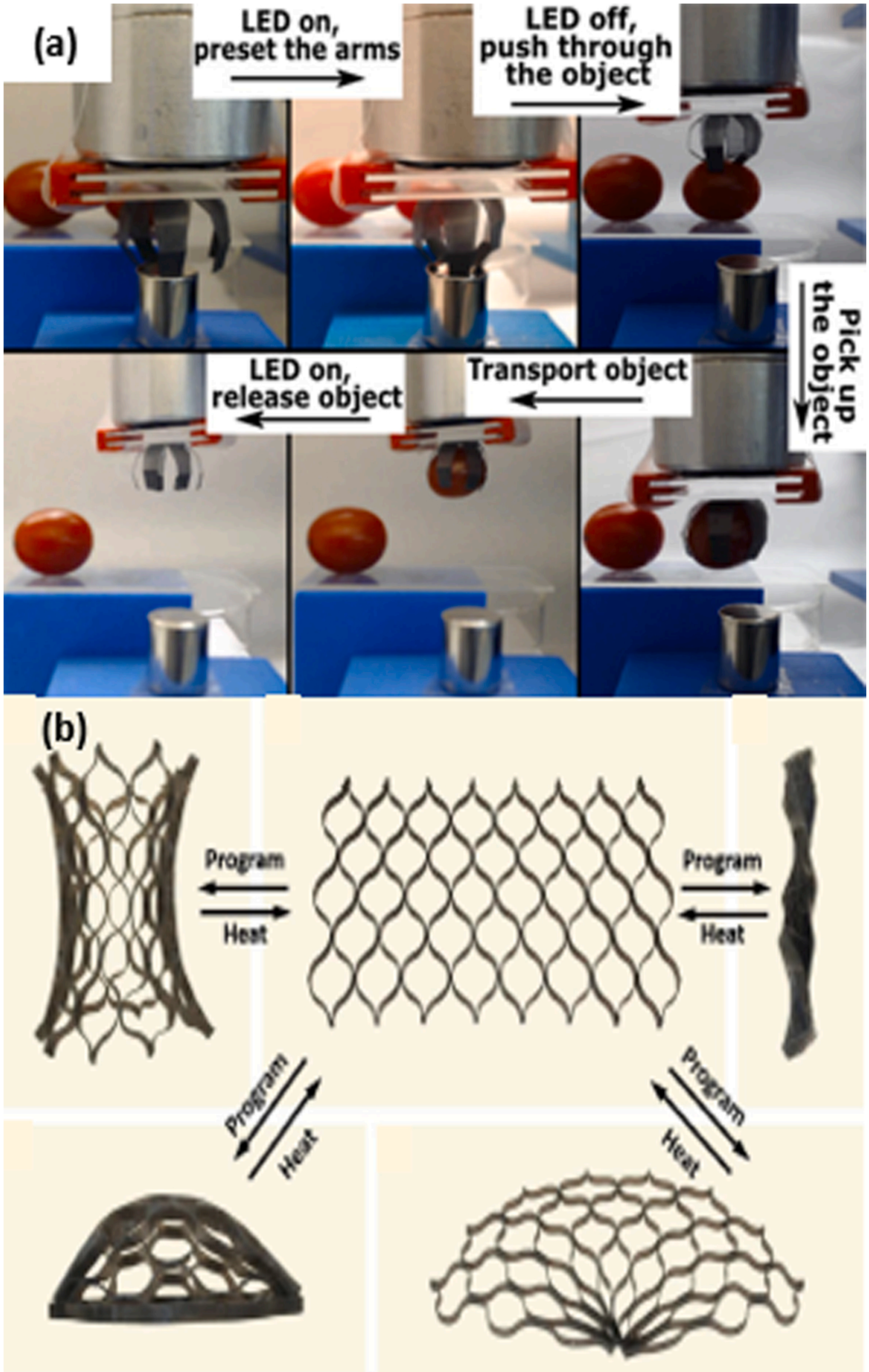

Fig. 6. Images of SMM-incorporated feasible 4D soft robots with 4D potential. (a) A soft robotic grabber to pick up, transport, and release small objects. The initial shape of the grabber is preset by the magnetic field, and the motion of the arms is controlled by switching on and off the LED. Image adapted from [50] with permission. (b) Different configurations of a thermo-responsive 4D printed construct. Image adapted from [52] with permission.

4. The vision of 4D Soft robots in biomedical engineering

Based on the working mechanisms mentioned above, 4D soft robots suggest infinite potential in biomedical applications. For example, as shown in Figs. 1 and 2f, the 4D printed brain and heart can be extremely useful as they were designed to precisely fit the surface curvature of the brain and heart under specific stimulation. 4D Soft robots that are fabricated with biological conformity possess capabilities for representative biomedical functions and mobility. These characteristics impel 4D soft robots to a variety of prospective technical advances in biomedical

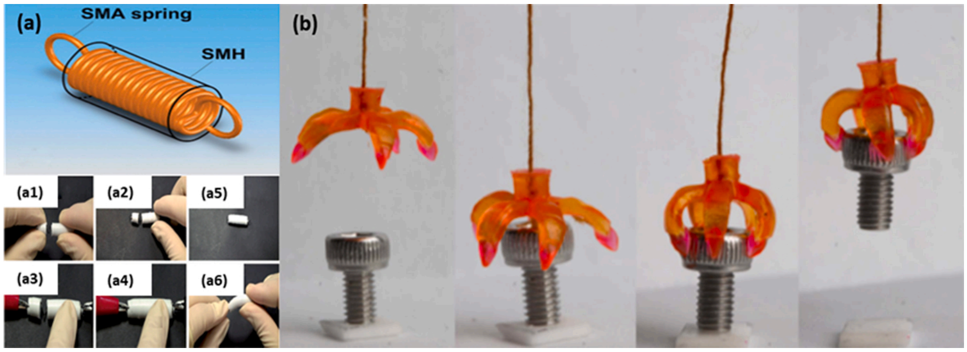

Fig. 7. (a) An illustration of SMH embedded self-healing SMA spring; (a1-a4) pulling apart SMH to fracture and joule heating SMA coil; (a5-a6) heated and bent sample. Image adapted from [40] with permission. (b) The sequential process of grabbing a screw by a 4D printed multi-material gripper. Image adapted from [59] with permission.

Table 1
Representative studies of 4D soft robotics at the current stage in summary.

Classification	Material composition	Fabrication technique	Actuation mechanism	Noticeable results	Limitations	Researchers
Shape memory materials	A crystalline shape memory polymer	A plasticity-based origami technique	Photothermal responsive	Programmability of spatial selective actuation Capability to isolate 3D shape and actuation Multiple stimuli responsive Outstanding flexibility	Absence of 3D printing technique Slow response to stimuli	Jin et al. (2018) [49]
	A one-way shape memory polymer with magnetic microparticles	A simple thin composite film	Photothermal / magnetic responsive	Multiple stimuli-responsive Quick transformation Potentially 3D printable	To obtain a reconfigurable behavior of the system, multiple stimuli need to be present simultaneously	Liu et al. (2019) [50]
	A naturally-derived novel liquid resin	Stereolithography 3D printing	Thermo-responsive	Directly 4D printable Highly biocompatible Quick transformation Transformation occurs at the human body temperature	Lack of physical strength	Miao et al. (2016) [51]
	A shape memory polymer	Inkjet and stereolithography 3D printing	Thermo-responsive	Directly 4D printable Various types of structures can be obtained Decent resolution	Pre-programming steps are required to actuate Slow response to stimuli	Ding et al. (2017) [52]
Combination of smart and conventional materials	A shape memory polymer and a photopolymerizable hydrogel	Stereolithography 3D printing	Thermo-responsive	Actuation speed can be controlled by varying blending ratio of the ink High resolution Programming and recovery occur around the human body temperature	Relatively slow response to stimuli and recovery	Ge et al. (2016) [59]
	A shape memory polymer and three types of hyperelastic polymers	Simple arrangement of bi-layered strips	Thermo-responsive	Various types of shape transformations can be obtained, such as rolled, spiral, wrinkled, and wave-like construct Simple steps to fabricate Potentially 3D printable	Not multiple stimuli-responsive More optimization process is required to obtain other complex shape transformations	Janbaz et al. (2016) [60]
	Carbon black liquid crystal elastomer and polyimide	Adhesion of thin layered films	Thermo-responsive	Instant actuation and recovery Complex shape programming is possible with independent add-on heaters	Due to the presence of heater, fabrication with 3D printing is questionable Complex design	Wang et al. (2018) [61]

engineering from miniaturized wearable soft robots to biologically inspired robots, contributing to numerous applications such as drug/cell delivery, sensing, minimally invasive surgery, and detoxification among others [4,62]. However, the current stage of transition from 3D to 4D soft robotics from a biomedical perspective is somewhat limited for most of the specific categories.

4.1. Current achievement

In general, 4D soft robots can be engineered for artificial tissue constructs [63]. In the study performed by Tasoglu et al., a paramagnetic responsive hydrogel was functionalized, and fabricated soft robots were self-assembled for functional patterns. They controlled the degree of magnetization of hydrogel with vitamin E to eradicate the free radicals for cell proliferation [63,64]. Recently, Miao et al. reported that a 4D printed substrate could influence cell behaviors and induce differentiation of stem cells [19]. Their 4D fabrication process involved a combination of printing and imprinting to provide neural stem cells with the particular differentiation microenvironments. In another study published lately, a 4D cardiac patch for the treatment of myocardial infarction printed by beam-scanning SLA was demonstrated [65]. Considering the physiological adaptability and biocompatible properties of the 4D printed hydrogel-based construct, the cardiac patch with a high degree of flexibility could take a volumetric change of the beating heart into account. A long-term in vivo study involving triculture of stem cells, stem cell-derived cardiomyocytes, and endothelial cells with the 4D printed patches resulted in significantly increased cell engraftment and vascularization in a murine chronic model.

Since the internal human body structure is complex, and reaching every nook and corner using conventional methods or materials is limited, advances in 4D soft robotics-based untethered microgrippers have gained attention as a significant development for more precise and minimally invasive surgery options. As opposed to traditional grippers for biomedical operations that lack mobility and exhibit size constraint issues, 4D soft robotics-based microgrippers are free from external power input and present superb mobility [4]. Yim et al. and Diller et al. designed a thermo-sensitive and untethered microgripper for a minimally invasive biopsy that was capable of self-folding and grabbing tissue [66,67].

4.2. Progress to overcome challenges

Features of 4D soft robots can also be utilized for monitoring unreachable areas and diagnosing disease in the human body [3]. 4D soft robots in micro-/nanoscale may flow through the circulatory system, as every site of the human body is reachable for blood [3,68]. They are expected to exhibit a potential capability for real-time detection and delivery of instant, vital information, as well as eradicating blood clots or plaque simultaneously. In the same context, targeted drug delivery by 4D soft robots can be implemented for therapeutic approaches. In contrast to conventional drug delivery mechanisms, targeted drug delivery can be significantly more effective in terms of selective regional therapy and thus can lower side effect risk in unaffected areas of the body. There have been many preliminary studies demonstrating micro-/nanorobotic drug delivery applications. For example, Mou et al. conducted a magnesium-based Janus micromotor for use in drug delivery through body fluid [69] where the drug delivery motion could be triggered and regulated by temperature control. Walker et al. introduced an enzymatically active magnetic micropropeller to penetrate through mucin gels [70]. In this study, they referenced the propulsion strategy of Helicobacter pylori through mucin gels to fabricate the artificial micropropeller. Although 4D printing approaches are not yet contained in this study, the enzymatically active micropropeller possesses the potential to incorporate the utilization of SMMs for more efficient magnetic actuation of drug delivery. Not just limited to drug delivery, the recent work performed by Yasa et al. exhibits the potential of 4D soft robotics for cell delivery in a similar manner. They 3D printed microscale stem cell transport soft robots that were steered by computational programming and a remotely controlled external magnetic field (Fig. 8) [2]. Their approach suggests another prospective scenario tied to 4D printing for further improvement, through the integration of a magnetically responsive lid to enhance sealing of encapsulated cells during and after propulsion.

4D soft robots could also serve as an innovative implementation of a detox process, while it is insufficient to incorporate the art of 4D printing at the current stage of technological advancement yet. In the same context as drug/cell delivery and sensing in the circulatory system, micro-/nanoscale 4D robots may sense and remove targeted toxins [4]. The previously mentioned study for cell delivery can be an extension for general detoxification by transporting red blood cells to the targeted area. Zhu et al. reported a method to engineer hydrogel-based catalytic propelling microfish to detoxify melittin [71]. Their experimental results have shown that the microfish in dynamic motion-promoted the detoxification process of melittin compared to the static condition. Similarly, Zhang et al. recently exhibited work for a self-propelled zinc oxide nanowire-based photocatalytic micro soft robot for pollutant degradation and detoxification [72]. The fabricated soft robot possessed the ability to shape change using different stretching ratios between polydimethylsiloxane (PDMS) and seed layers. Despite the absence of 4D printing, these studies imply the future of 4D soft robotics for use in detoxification, because 1) their primary propelling systems rely on self-propulsion, 2) shape change is the main source to promote pollutant degradation and detoxification.

5. Conclusions and future directions

4D printing possesses remarkable benefits for the fabrication of soft robots with complex external and internal designs. A diverse series of versatile techniques and materials have been developed to integrate the two ingenious techniques of 4D printing and soft robotics in the micro-/

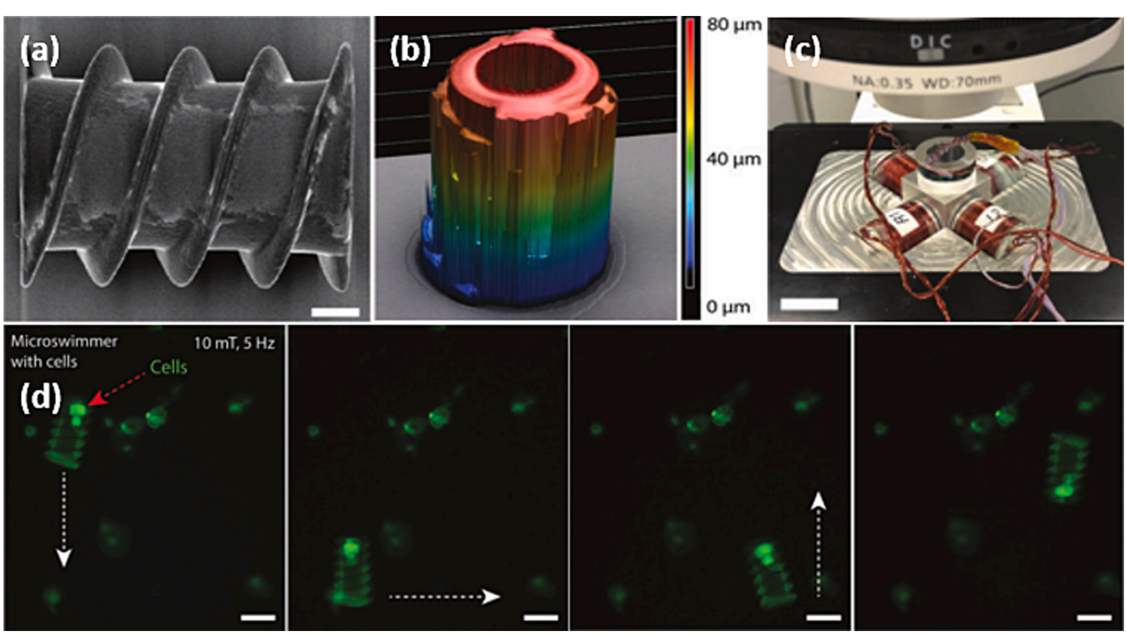

Fig. 8. (a) A scanning electron microscope image of the 3D printed microscale stem cell transport. Scale bar, 10 µm. (b) A 3D laser scanning micrograph of the 3D printed microscale stem cell transport. (c) A photo image of the actuation setup of the microscale stem cell transport. Scale bar, 3 cm. (d) Sequential images of the actuation of microscale stem cell transport with cells encapsulated. Scale bar, 50 µm [2]. Images adapted from [2] with permission.

nanoscale, for use in biomedical applications. The initial design and fabrication of 4D soft robots to properly propel at such sub-microscales essentially begin with the selection of materials. These materials are either chemically reactive and/or decomposable, and as such are capable of steering 4D soft robots that actively respond to certain stimuli to accelerate the systemic transition from symmetric to asymmetric. Based on the generated locomotion by a suitable power supply, the fabricated 4D soft robots are capable of conveying their biomedical tasks inside or outside of the human body.

The main approaches to fabricate 4D soft robots predominantly rely on the selection of SMMs at the current stage of technical advancement, which means the mechanical properties of the designed micro-/nanorobots are essentially determined before fabrication begins. Specifically, SMPs occupy the biggest portion of SMMs for fabricating soft robots using 4D printing because of their biochemical and mechanical properties. In order to diversify the type of SMMs to use in 4D soft robotics, regulated and advanced research on other SMMs is required. Moreover, demonstrating 4D soft robots with only SMMs offer mostly one way or limited numbers of reversible actuation. In order to overcome these limitations, researchers have focused on thermomechanical programming of 2D/3D printed or 4D printable materials to allow the freedom of reversible actuation. However, this approach is also considered incomplete for fully incorporating 4D printing due to the lack of optimized protocol for programmable materials to obtain unlimited reversibility using achieved anisotropic stresses.

Due to the aforementioned challenges, such as a limited selection of materials to fabricate 4D soft robots, commercial use of soft robotics still has a way to go to full maturity. Along with the material selection, diversification of fabrication technique is currently urgent. The commercialization of 4D soft robots for biomedical engineering would require a huge prospective effort to answer many unresolved questions. In order to operate soft robots at micro-/nanoscales in the human body, where large barriers to motion such as inconsistent and dynamic biological environments exist, accurate optimization and repeated testing are critically required [4]. Among the potential applications in biomedical engineering, 4D soft robots for minimally invasive surgery, such as untethered microgrippers, is currently the most feasible method for integrating this technology. Although the aforementioned sample studies were not fully 4D printing incorporated, they presented a huge potential for torque or force-based and magnetic responsive microgrippers to be used for *in vivo* or *ex vivo* experiments [66,67]. In contrast, employing 4D soft robotics for biosensing and detoxification remains in the early stages due to the complex structure of the human body, requiring further investigation of autonomous operation as well as biocompatible and biodegradable materials [71–74]. However, since there are many ongoing studies to utilize soft micro-/nanorobots as delivery vehicles, including targeted drug and cell transport to couple current techniques and 4D printing, the collective technique should be further explored in the near future.

Considering the future of 4D soft robotics, implementable, technical development is critically required to be practical in the field of biomedical engineering. Reliable methods to fabricate 4D soft robots cannot be acquired from a partial understanding of a certain research area. Therefore, a thorough and integrated understanding of material science, mechanical engineering, and biomedical engineering is highly recommended for researchers to develop a comprehensive protocol for fabricating and implementing 4D soft micro-/nanorobots.

Declaration of Competing Interest

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

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