

4D printed shape memory polymers and their structures for biomedical applications

LI YueJia¹, ZHANG FengHua¹, LIU YanJu² & LENG JinSong^{1*}¹ National Key Laboratory of Science and Technology on Advanced Composites in Special Environment, Harbin Institute of Technology (HIT), Harbin 150080, China;² Department of Astronautical Science and Mechanics, Harbin Institute of Technology (HIT), Harbin 150001, China

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Shape memory polymers are smart materials that produce shape changes under external stimulus conditions. Four-dimensional (4D) printing is a comprehensive technology originate from deformable materials and three-dimensional (3D) printing technology. At present, 4D printed shape memory polymers and shape-changing structures have been applied in various fields, especially in the field of biomedical science. 4D printing technology has made a breakthrough of personalized customization in the traditional medical field, providing a new direction for the further development of the biomedical field. In this review, the recent research and development of shape memory polymer, 3D printing technology, 4D printed shape memory polymers and shape-changing structures in biomedical area are present. The examples and applications of 4D printed shape memory polymers and their structures in the area of biomedical are also introduced. Based on 4D printing, stimulated by different conditions, 3D printed objects can be fabricated into various biomedical applications such as cell scaffolds, vascular stents, bone scaffolds, tracheal stents and cardiac stents by different 3D printing techniques. Finally, the application prospects, existing technical restriction and future development directions of 4D printed shape memory polymers and their structures in the biomedical field are summarized.

4D printing, shape memory polymers, shape-changing structures, biomedical applications

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1 Introduction

Shape memory polymer (SMP) is a kind of novel new type material that retains its temporary shape under external forces and change when stimulated, then returning from the temporary shape to its original shape to complete a shape memory cycle. According to the shape memory mechanism, the shape memory polymer also displays the non-thermal triple shape memory effect (SME) and the reversible SME, which can realize memory multiple shapes and reversible deformation as shown in Figure 1 [1]. SMPs have characteristics of lighter weight, stronger recovery performance,

milder recovery conditions, biodegradability, low biotoxicity and even no toxicity [2–6]. SMP was originally a kind of polynorbornene film, developed by CdF Chime Company, France, in 1984. With the advent of the first SMP, more excellent SMPs have been developed and shown great potential allocation value in many fields. At present, SMPs have been applied in various fields, such as aerospace [7,8], additive manufacturing [1], clothing materials, biomedical science [9–11]. The excellent performance of SMP makes it particularly useful in biomedical applications such as SMP sutures, SMP dental appliances, SMP aneurysm occludes. The structures of these SMPs are mostly simple linear structures. Traditional preparation techniques are difficult to achieve structures that are relatively complex, in-

*Corresponding author (email: lengjs@hit.edu.cn)

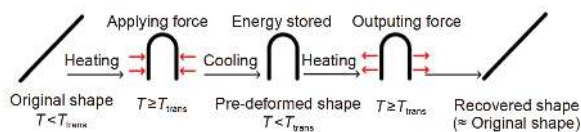


Figure 1 (Color online) Schematic illustration of the SME [1].

dividualized, and highly accurate structures such as cardiac stents, bone stents, and tracheal stents. The emergence of four-dimensional (4D) printing complements this deficiency.

In February 2013, Tibbitts [12,13] from MIT first presented the idea of “4D printing” technology at the TED conference and presented the 4D printing research results. Through the combination of SMP and three-dimensional (3D) printing technology, the technology of using SMP for 3D printing to form 4D printing came into being. SMP can interact with the stimulus conditions, so the 4D printed SMP structure can produce corresponding shape changes after external conditions (such as temperature, humidity, current, magnetic, pH) [14,15]. Since the success of 4D printed SMP structure, more and more researchers have invested in the research of 4D printed SMP. With the continuous development and maturity of 4D printing technology, the advantages of 4D printed SMP structure are more obvious [16–22]. 4D printing technology can realize complex personalized biological organs or tissues by printing a variety of biomedical stents, such as bone stents and vascular stents, applied to the repair of bone tissue or thrombus which provide more solutions for patients [23,24]. Studies have shown that 4D printed SMP can not only perform simple shape memory process, but also achieve various functions such as self-deformation, self-assembly, self-healing, by pre-setting the deformation scheme (including target shape, performance, functions, etc.) [25–30]. At present, 4D printed SMP methods mainly include fused deposition modeling (FDM), stereo lithography apparatus (SLA), polymer jet technology (PolyJet), and direct-writing (DW). 4D printed SMP has been used in many industries, such as aerospace, electrical automation, robotics, textile materials, tissue engineering, medical devices, drug delivery carriers and other fields [31–35].

With the improvement of technique, 4D printing has realized the application of printing structures at different scales as shown in Figure 2. As for the developing in nozzle diameter in DIW printing, 4D printing can be used to manufacture nano-sized structures, also microscale and macroscale structures [36]. Printing speed and resolution affect the chemical, physical properties and complexity of the material. Kim et al. [37] first proposed the nanoscale 3D printed smart nanocomposite in 2014. Mu et al. [38] successfully used the DIW printing method to achieve nanoscale 4D printing in 2017. In August 2016, MIT Ge et al. [19] used high resolution projection micro-stereolithography (PμSL) printing technology, used a series of photo-curable metha-

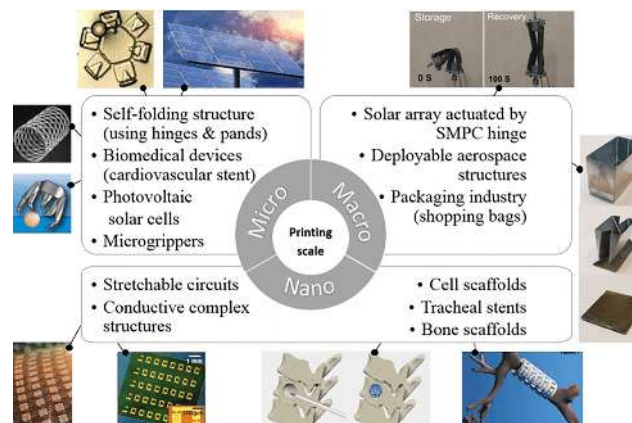


Figure 2 (Color online) Application of 4D printing structures in different scales.

crylate, to achieve 4D printing of multi-material shape-changing structures with micron-scale resolution for the first time. Successful development of 4D printers operating on nanoscale, microscale and macroscale will be used to construct biomedical devices [39,40], deployable aerospace structures [1,41], shopping bags [42] and morphing photovoltaic solar cells [43,44] and other practical applications, promoted the design of SMP 4D printing structures.

At present, 4D printed SMP has achieved a series of remarkable results in biomedical applications such as biological engineering, medical devices, drug delivery carriers. With the increasing requirements for complex structures, personalized implant device and high-precision medical devices, the emergence of 4D printing technology is expected to breakthrough the technical plateau of smart materials and structures in the biomedical field and become a new bond for future cooperation between various disciplines. This paper mainly reviews the application of 4D printed SMP and shape-changing structures with their composite materials in biomedical fields. As shown in Figure 3, based on 4D printing, stimulated by different conditions, 3D printed objects can be fabricated into various biomedical applications such as vascular stents, tracheal stents, cell scaffolds, bone scaffolds, cardiac stents and occlusion devices by different 3D printing techniques. Then we summarize the applicable materials, preparation techniques, actuate methods and main applications of 4D printed SMP in this field. Furthermore, we analyze the existing problems and future developments in the application of 4D printed SMPs and shape-changing structures in biomedical field.

2 4D Printed SMP biomaterials

2.1 SMP biomaterials

SMP is a kind of smart functional novel material, and its applications in the biomedical area are receiving more and

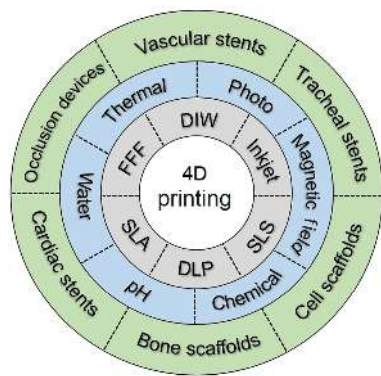


Figure 3 (Color online) Based on 4D printing, stimulated by different conditions, 3D printed objects can be fabricated into various biomedical applications by different 3D printing techniques. The elements and the categories involved in 4D printing are shown. (1) 3D printing technology: FFF, DIW, SLS, DLP, SLA, and inkjet; (2) the stimulus for 4D printing: thermal, light, chemical, pH, water, and magnetic field; (3) biomedical applications for 4D printing: vascular stents, tracheal stents, cell scaffolds, bone scaffolds, cardiac stents, occlusion devices and other applications.

more attention. Different from shape memory alloys and ceramics, shape memory polymers and their structures have the advantages of high shape recovery rate, adjustable shape memory temperature, colorable, large deformation, shape-shifting ability, low density and low cost. In particular, shape memory polyurethane (PU) has the advantages of structure-performance controllable, selectable of shape memory temperature range (-30°C to 70°C), good biocompatibility, etc., and thus has great application prospects in the biomedical field. Polycaprolactone (PCL) has good biocompatibility, organic polymer compatibility and biodegradability. It can be used as cell growth support materials. With good shape memory performance, it can be used in the field of biomedical. As a biocompatible and biodegradable material, polylactic acid (PLA) can also be an environmentally friendly material for biomedical applications. However, the SMPs that have been researched so far still have a lot of room for improvement in terms of overall performance. Research shows that polynorbornene can be deformed rapidly, has large deformation recovery force, and has high deformation recovery precision. However, its shape recovery temperature can be adjusted to a small range, and the relative molecular weight is large, so the molding process has a certain difficulty [9,45]. In addition, most SMPs cannot be deformed rapidly, with small shape recovery force, low recovery accuracy, unsatisfactory repetitive memory effects, and insufficient mechanical strength and chemical durability. Therefore, the use of molecular design and material modification technology to optimize its shape memory function, and to improve its comprehensive performance, is the key to the research and development of shape memory materials in the future [46].

SMPs used in the biomedical field generally have a shape changing temperature close to body temperature [47–52], a

mild shape changing process, good biocompatibility, low bio-toxicity and even some of them have biodegradability [50,51,53–55].

2.2 4D printing technology

4D printing technology is an emerging manufacturing technology originate from additive manufacturing (3D printing) technology and smart materials, which makes 3D printing structure raise a level in terms of shape, performance and function. 4D printing technology is a time-dependent technology that can be used to produce predictable material and is independent of the printer. Structures with specific properties, such as self-assembly, multi-function and self-healing can be manufactured by controlling the 4D printing technology, and then they can be applied to various fields [56]. 4D printed SMPs are developing in the direction of controllable morphology and specific actions. With the development of raw materials, forming methods, software control and machine precision, 4D printing technology is developing rapidly, and it is gradually becoming intelligent, precise and efficient.

Zhou et al. [57] proposed four main 4D printing methods and briefly discussed the main features of these methods. The four methods are: element self-assembly; deformation mismatch; bi-stable and SME. Fundamentally, 4D printing is closely related to the manufacturing techniques of some complex structures, including expandable mechanisms, bi-stable structures, flexible mechanisms, and automated assembly structures and automated disassembly structures. Specific technical aspects include stimuli-induced deformation mismatch and deformation techniques based on SME. Sydney Gladman et al. [58] mixed cellulose fibers extracted from wood pulp with acrylamide hydrogel (a gel that swells and expands in water), and adds a fluorescent dye to make a new type of 4D printing. The material, which contains many tiny colloidal fibers, can be changed in hardness and water solubility according to different arrangements. After “coding”, the printed object becomes a more complex shape (Figure 4). In 2016, researchers at Georgia Tech, Xi’an Jiaotong University, and Singapore University of Science and Technology [59] used environmentally sensitive SMPs for 3D printed hydrogels, allowing the shape-changing structure to reversibly switch between two stable states without mechanical load training.

In terms of printing technology, Ge et al. [19] proposed a new 4D printing method to enable high resolution printing of multi-material SMPs. They designed a network of methacrylate-based copolymers that were light-curing and used for high-resolution projection microlithography to enable the printing of shape-changing structures with controlled thermal behavior. In 2017, Miao et al. [47] prepared a 3D biomedical scaffold using soybean oil epoxidized acrylate

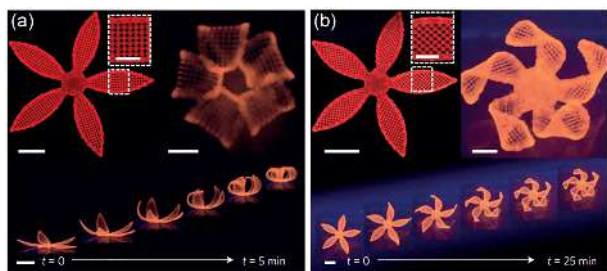


Figure 4 (Color online) 4D printed morphology flowers composed of $90^\circ/0^\circ$ (a) and $-45^\circ/45^\circ$ (b) bilayers oriented with respect to the long axis of each petal, with the swelling process in different orientations (scale bars, 5 mm, inset scale bars 2.5 mm) [58].

(SOEA). The scaffold has good shape memory properties and can play the role of 4D printing technology. Moreover, the scaffold has good biocompatibility with human bone marrow mesenchymal stem cells so that it can be applied in biomedical field. They make a great development of renewable vegetable oil and 4D printing technology in the biomedical field. In 2017, 4D printing technology also has significant research progress in applied science and engineering. Naficy et al. [35] used a series of thermosensitive hydrogel inks to establish a simple model for 3D printing. Using this model, they predict the bending properties of printed structures, including bending curvature and bending angle.

Zhang et al. [60] designed a series of braided tube preforms that used shape memory polylactic-acid as material and was molded by FDM 4D printing. The braided tube preform is a multi-directional reinforced textile preform as shown in Figure 5. The thermomechanical properties and shape recovery of the samples were characterized by making

different braid angle samples, wall thickness samples, and by designing different transition temperatures. They also printed composites of braided tubes/silicone elastomers, providing new directions for novel functional composites. Also using FDM 4D printing, Liu et al. [61] 4D printed laminated Miura-origami tessellations and tubes using SMP polylactic-acid filaments. The folding and shape recovery process of the sample under the induction of compression load was studied. The results of the study showed that the sample exhibited high shape recovery ability with a shape recovery rate of more than 94% and volume change up to 289%. The structure can be applied to actuators and reconfigurable devices with good development prospects.

3 Applications of 4D printed SMP in biomedical field

4D printed SMPs with complex structures can be used in biomedical field, such as cell scaffolds, vascular stents, bone scaffolds, tracheal stents, cardiac stents and occlusion devices.

3.1 Cell scaffolds

Cells are an important basis for construction organs or tissues. In just a few decades, significant progress has been made in the research and development of cell scaffolds. Some researchers have used 4D printed cell scaffolds in clinical through FDM, SLA and other printing methods using raw materials such as castor oil and soybean oil.

Miao et al. [47] used 3D photocuring printer and new re-

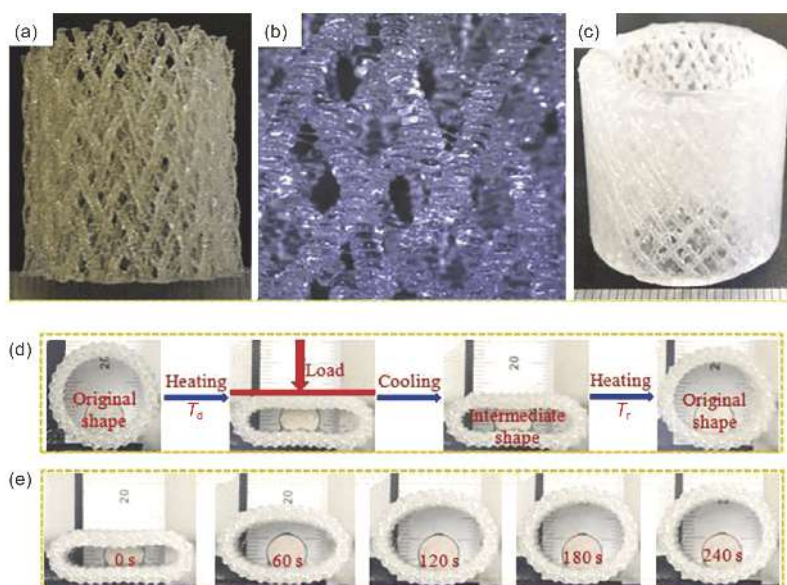


Figure 5 (Color online) 3D circular braided tube specimens with braiding angle of 30° and three braiding layers: (a) 4D printed circular braided tube preform; (b) enlarged optical image of preform surface; (c) 4D printed circular braided tube preform/silicone elastomer matrix composite. Shape memory cycle: (d) 4D printed circular braided tube; (e) the specimen A30L3T70 [60].

newable SOEA material to print a shape memory scaffold that can support the growth of human bone marrow mesenchymal stem cells (hMSC), which has shape memory function and high biocompatibility. Shape memory experiments showed that the stent can be kept in a temporary shape at -18°C under the external force. When the scaffold is placed in the body, reached body temperature (37°C), it will automatically return to the original shape that we need as shown in Figure 6. Cytotoxicity analysis showed that the novel shape memory scaffold was not cytotoxic. Compared with traditional polyethylene glycol diacrylate (PEGDA) scaffold, the scaffold shown in this study has a significant effect on the adhesion and proliferation of hMSC.

Using biomaterial shape memory PU and 4D printing technology, Hendrikson et al. [48] successfully printed two shape memory holders ($0/90^{\circ}$ and $0/45^{\circ}$) that stimulate the morphological changes of cells. The mechanical strength test, the shape memory characterization and the cell activity were studied. The thermomechanical strength analysis showed that the temperature of the two stents activated SME was 32°C , indicating that T_g (glass transition temperature) was not affected by the fiber alignment direction. The stent was placed in a 65°C environment. An external force was applied to obtain a temporary shape and the stent was fixed by cooling at 4°C . The cells were seeded on a scaffold. The sample was cultured at 30°C to adhere the cells to the scaffold and proliferate the cells. The temperature was raised to 37°C to gradually return the stent to the original shape. The determination of the characterization shows that the permanent shape of the two types of structures has good recovery ability. The $0/45^{\circ}$ stent exhibits higher shape recovery ability due to the different fiber arrangement directions of the two stents.

Cell viability studies conducted for 14 days showed that

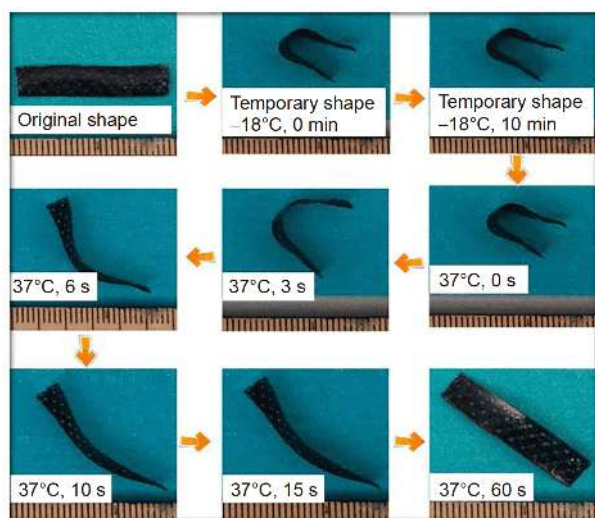


Figure 6 (Color online) The deformation process of the shape memory bracket (dyed in black to enhance contrast with the background) [47].

the cell viability on both scaffolds was completely normal. The cells are inoculated on the scaffold for culture, then the cell scaffold gradually returns to the original shape during the culture process, and the cells grow along the stretching direction of the two scaffold fibers after the shape is restored, exhibiting an elongated state. The elongations were calculated according to the parameters of cell deformation to be 0.36 and 0.23, respectively (spherical is 1) as shown in Figure 7(i) and (j). The 4D-printed SMP cell scaffold can mechanically stimulate the cells through shape recovery, leading to the directional growth of cells and nuclei. Adherent cell morphology can be changed by a single mechanical stimulus. It is shown that the scaffold has good cell compatibility.

Miao et al. [49] synthesized a novel SMP by chemically crosslinking natural derivatives castor oil with polycaprolactone triol and polyisocyanate. Using this new SMP combined with PLA for 4D printing, a tissue scaffold with SME and high biocompatibility was prepared. The stent also exhibits a biomimetic gradient void structure over time. The mechanical properties of the scaffold show that the porosity of the scaffold can be achieved by changing the packing density of the new SMP. The higher the packing density, the more voids will appear after PLA degradation. The scaffold has a diameter of 5 mm and the distance between the gaps of $240\ \mu\text{m}$ to $560\ \mu\text{m}$ as shown in Figure 8(a). The gaps are distributed in a gradient from top to bottom. This gradient void is a gradient of the simulated natural tissue, and the tissue cells can grow inward. The gaps are interconnected to deliver the nutrients needed for cell growth, as well as the waste generated by the cells.

Shape memory performance analysis showed that the tissue scaffold T_g ranged from -8°C to 35°C . The scaffold was prepared into a temporary shape at -18°C and returned to its original shape in an environment of body temperature with a shape recovery of 92%. Scanning electron microscopy showed that the tissue scaffold had a gradient micro-empty structure. Cell culture experiments showed that with the PCL scaffold as the control group, the gradient void tissue scaffold showed adhesion to MSC and induced cell proliferation and differentiation.

Hsiao et al. [50] synthesized biodegradable PU dispersions by a waterborne process and introduced acrylate group to make the PU chain becomes to light sensitive and heat sensitive parts during cross-linking, which improve the printability of the material, enables dual stimuli-response as shown in Figure 9(a). The heat-sensitive segment allows the PU dispersions to be rapidly thermal gelation with gel moduli as it approaches body temperature, and the light sensitive segment allows the material to form a compact packing structure upon heating. Dual response allows for greater precision, better cell differentiate and proliferation, and facilitates the printing of soft tissue based neural stem

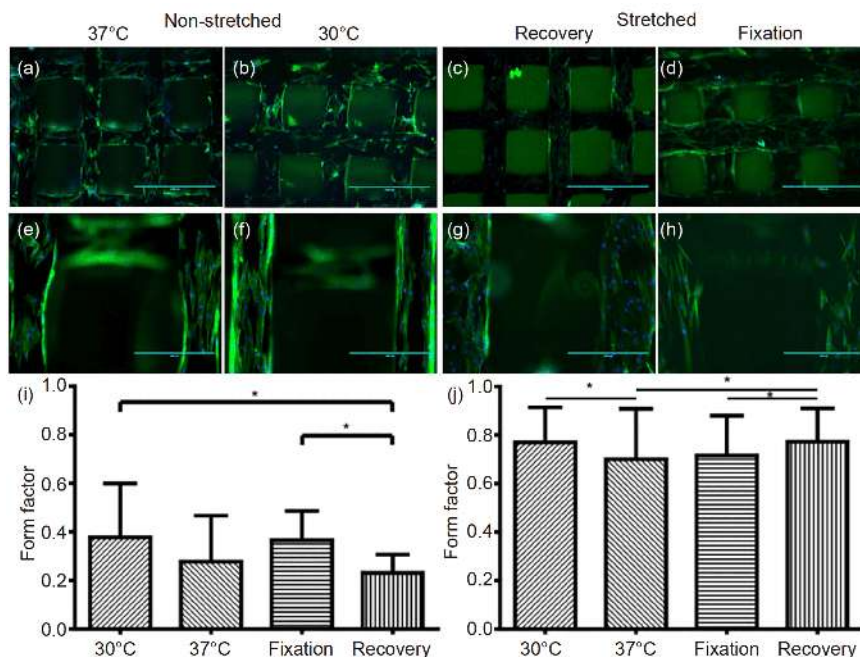


Figure 7 (Color online) Staining of seeded cells on stretched ((c), (d), (g), (h)) and unstretched ((a), (b), (e), (f)) scaffolds. Scale bar: (a)–(d) with 1000 μm ; (e), (f) with 500 μm ; (i), (j) is the elongation calculation of cell shape and nuclei [48].

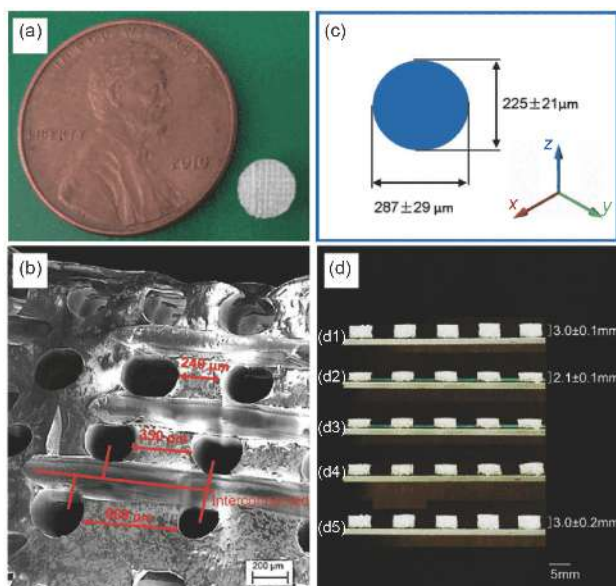


Figure 8 (Color online) (a) The scaffold compared to a cent; (b) SEM image of pore distribution in the scaffold; (c) pore size distribution; (d) deformation process of five different density tissue scaffolds: (d1) the original shape of the scaffold; (d2) temporary shape at -18°C ; (d3) 0 s at 37°C ; (d4) 10 s at 37°C ; (d5) 3 min at 37°C . [49].

cells.

Miao et al. [49] used a photolithographic-sterolithographic-tandem strategy (PSTS) and SOEA ink to print a new 4D layered heart cellular patch, as shown in Figure 10, for effectively regulate the myocardial cell behavior of hMSC. The scaffold produced could induce cell proliferation

and differentiation and was confirmed by immunofluorescence staining and qRT-PCR analysis. Miao et al. [47] also developed a new multi-stimuli-responsive (solvent stimuli-, laser stimuli-) SMP through stereolithography 4D printing. A multi-response intelligent architecture was realized by using nano-fibrillated cellulose reinforced SOEA. This work guides the development of new 4D printed biomedical scaffolds in the future.

The cell scaffold prepared by 4D printed SMP can induce cell proliferation and differentiation. Miao et al. [47] synthesized a new renewable SOEA material from the material, which enhanced cell adhesion and proliferation compared with traditional PEGDA. Hendrikson et al. [48] began to prepare two cell scaffolds in the direction of fiber alignment by changing the orientation of the fibers in the scaffold. It was shown that the deformation of the cell scaffold produces mechanical stimulation of the cells, which can lead to the directed growth of cells and nuclei. Miao et al. [49] prepared a branch with a bionic gradient void structure from the internal structure of the scaffold. The cells can extend into the ingrowth of the voids, and the voids can also serve to transport nutrients and metabolize waste. These examples have developed and tested some of the excellent properties of 4D printed shape memory cell scaffolds from different perspectives. Currently, there are few SMP types that are suitable for 4D printing and have high biocompatibility. Through the development of 4D printing technology and highly biocompatible intelligent biomaterials, the research and development of new functional biomedical stents will be guided.

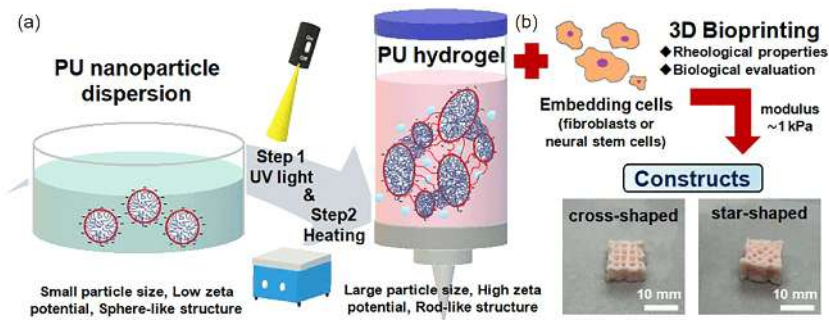


Figure 9 (Color online) (a) Schematics showing the mechanism for the dual stimuli-sensitive PU in response to UV treatment and subsequent heating; (b) appearance of the constructs of PUA3 hydrogel fabricated by a 3D bio-printer using two different types of deposition paths (cross-shaped and star-shaped deposition) [50].

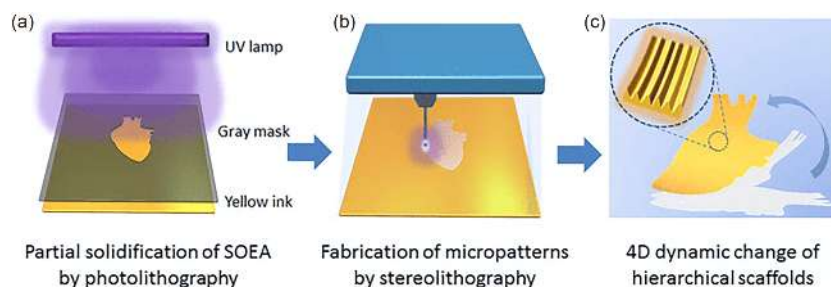


Figure 10 (Color online) Schematic of the photolithographic-stereolithographic-tandem process. (a) The exposed heart-shaped yellow ink was partially solidified under UV lamp; (b) micropatterns are drawn using a laser head on the unsolidified ink film forming hierarchical structures; (c) the 4D performance of the flat scaffold under external stimulus [49].

3.2 Vascular stents

Intravascular stent is a tubular structural device used to support stenotic or occluded blood vessels, mostly made of stainless steel wire and Nitinol. We demonstrate the application of SMP biomaterials in vascular stents, which has the advantages of biodegradability and low bio-toxicity. Intravascular stents can solve many difficult problems. Therefore, this technology is more and more popular in clinical applications. At present, the printing of vascular stents mostly uses DIW, SLA and FDM printing methods.

Meyer et al. [52] structured α,ω -polytetrahydrofuran-ther-diacrylate (PTHF-DA) resins by stereolithography and performed multiphoton polymerization structuring to obtain oligomers with SME, biocompatibility and non-toxicity. This material can be used for blood vessel-like supporting structures, self-tidying sewing thread as shown in Figure 11. The SLA print stents allow precise control to the dimension of μm for better control of porosity and structure.

Wei et al. [23] added magnetic Fe_3O_4 nanoparticles as functional particles to PLA to prepare a shape memory composite that can be deformed by magnetic stimuli. The spiral intravascular stent structure based on this material for direct-writing is self-expandable triggered by a magnetic field and complete the unfolding process within 10 s in Figure 12(f). In this study, the Fe_3O_4 nanoparticles make the

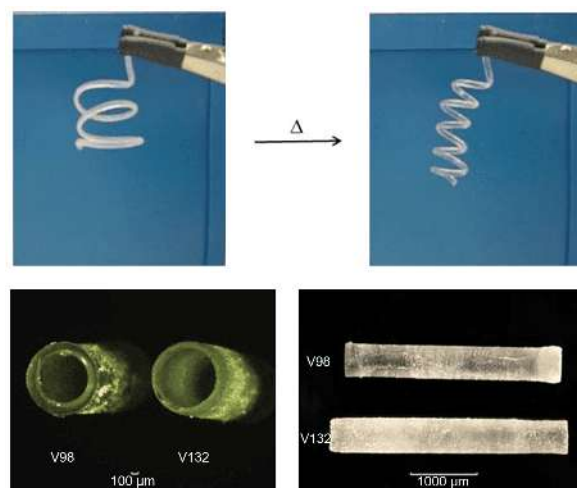


Figure 11 (Color online) Photographs of PTHF-DA shape memory microtubes printed via SLA. Shape changes can occur at room temperature and -20°C [52].

PLA able to be magnetically actuated. Self-expanding vascular stents prepared with this material can be driven without contact. Direct-write (DW) printing techniques designed a personalized vascular stent model for patients.

Self-expandable vascular stent can be used to treat cardiovascular diseases such as vascular stenosis in coronary heart disease caused by thrombus. When the self-expanding

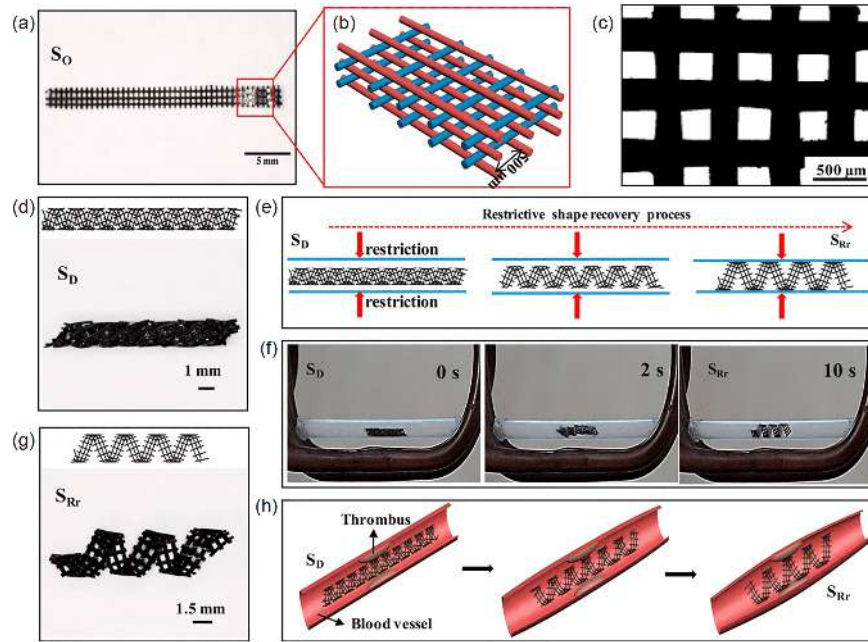


Figure 12 (Color online) Schematic of deformation of 4D printed shape memory vascular stent under the stimulation of external magnetic field. (a)–(d) and (g) Schematic of the scaffold; (e)–(f) shape recovery process under restrictive circumstance and magnetic field, respectively; (h) the application of vascular stent [23].

vascular stent reaches the stenosis of the vascular, the stent is actuated by an external alternating magnetic field, then the diameter of the vascular stent is enlarged to support the stenosis. After that, the vascular allow the blood to circulate normally. Even the structure of the vascular stent is relatively simple, the magnetically stimuli composite materials and 4D printing technology have great potential in the field of biomedical science. This technology not only realizes the intelligent remote control of medical devices, but also opens up new possibilities for minimally invasive surgery. It has great application prospects in the intelligentization and personalization of human implanted devices and is also of great significance for the further progress of biomedical fields.

Kuang et al. [62] synthesized a highly stretchable and flexible photocurable ink with polyurethane diacrylate and semi-crystalline polymer. Intelligent functional elastomers with shape memory performance and self-healing properties were fabricated by UV assisted DIW 3D printing, as shown in Figure 13. Shape memory experiments show that the elastomer has a deformation rate of up to 600% after rising to the shape changing temperature. This SMP with good shape memory properties can be applied to clinical fields such as vascular repair, vascular occlude, in the future. 4D printed SMP technologies provide a research basis for the development of soft robots and intelligent biomedical devices.

Wu et al. [53] FDM 3D printed a PLA vascular stent with a negative Poisson's ratio (NPR) structure and studied the effect of the arrowhead NPR structure on the radial compression

performance of the vascular stent. As shown in Figure 14(a), the NPR structural unit is drawn by Autodesk Computer Aided Design along the axis and circumferential directions to design a vascular stent, which flat and three-dimensional model are shown in Figures 14(b) and (c), respectively. The stent of this kind of structure has better radial compression performance and allows the length and diameter to simultaneously shrink and expand, which is beneficial to the minimally invasive surgery and better to the vessel walls. Figure 14(d)–(f) shows the shape memory process of the PLA stent, with both diameter and length recovery rates above 95%.

Liu et al. [63] based on DIW 3D printed an active thermoresponsive gel (pNIPAM) and a passive immobilize non-responsive gel (polyacrylamide; pAAM) gel tube, complex shape changes and motions such as bending, clamping, elongation and radial expansion, are achieved by the combination of segmented 3D printed expanded and non-expanded materials. Tubular materials are common in many organisms and this combination technique can be applied to vascular implants and soft robots with thermal response. This novel technology combines finite element simulation with 3D printing and combines active and passive stimulus response materials to make shape-changing structures more possibilities.

Wan et al. [36] successfully used poly(D,L-lactide-co-trimethylene carbonate) (PLMC) for DIW 3D printing for the first time by changing the viscosity of the ink. They print the structure from 1D to 3D with a shape recovery rate of up to

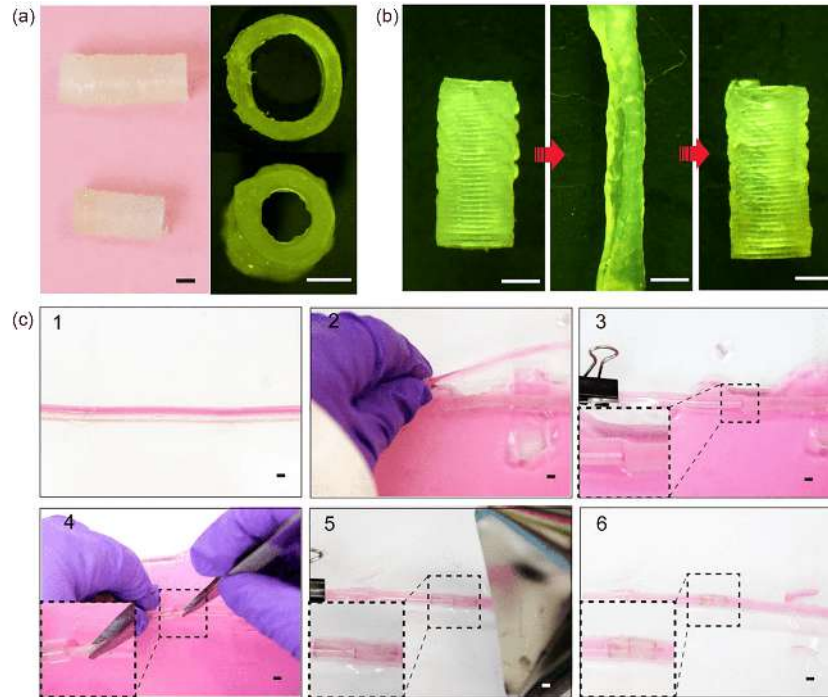


Figure 13 (Color online) (a) and (b) DIW printing of semi-IPN SM tube for vascular repair; (c) operation in biomedical application [62].

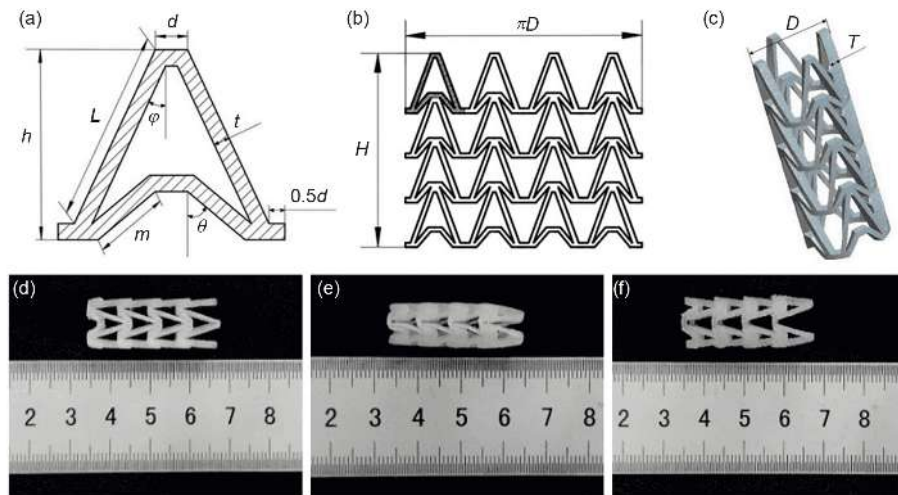


Figure 14 (Color online) Vascular stent model with NPR structure: (a) arrowhead NPR structure unit; (b) stent flat developing drawing; (c) three-dimensional model of stent. The geometry of the vascular stent can be defined by the size parameters: L represents the length of the support strut; m represents the length of the re-entrant strut; h represents the height of the unit; t represents the width of the strut; d represents the width of the link; φ represents the angle between the support strut and the axial direction; θ represents the angle between the re-entrant strut and the axial direction; D represents the outer diameter of the vascular stent; H represents the total length of vascular stent; T represents the thickness of the stent. Shape change of 3D printed PLA vascular stent with NPR structure: (d) original PLA stent; (e) crimped PLA stent; (f) recovery PLA stent [53].

99.98%, a low actuation temperature of 40°C–45°C and a fast response time from 3–4 s (1D–2D) to 35 s (3D–4D). This material is suitable for biomedical applications such as surgical sutures and 4D stents. The vascular stent shown in the Figure 15 can be recovered at a temperature close to body temperature, and the recovery process is mild. The results also laid the foundation for future applications in soft robots and electronic medical applications.

3.3 Bone scaffolds

Biodegradable bone scaffold fabrication has always been the focus of tissue engineering. Some researchers have used FDM to print porous bone scaffolds using materials such as PLA. The biomaterials have mild recovery conditions and meet the performance requirements of implanted bone.

Senatov et al. [64] mixed PLA with hydroxyapatite (HA) in

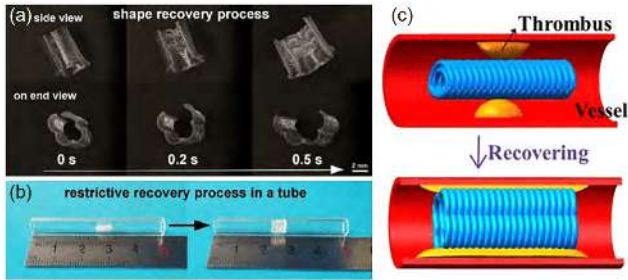


Figure 15 (Color online) 3D scaffold. (a) Macroscopic shape memory behavior of the scaffold within 0.5 s; (b) restrictive shape recovery process in a PMMA tube; (c) schematic diagram of restrictive shape recovery behavior exhibiting potential as an intravascular stent [36].

a mass ratio of 20:3 and printed a porous scaffold with shape memory function for bone defects by FDM. The properties of mechanical properties, structural properties and SMEs were tested. The HA particle ordering process is to be dispersed in the PLA molecular chain to form a rigid fixed phase, which reduces the fluidity of the molecule, resulting in a material's T_g rising from 53°C to 57.1°C. The shape memory test proves that the recovery stress of the stent is increased. The PLA/HA porous scaffold was subjected to 3 cycles of compression-heating-compression without delamination, and the highest shape recovery rate was 98%. The SME of the porous PLA/HA scaffold can be used as a self-fitting implant for repairing bone defects. Figure 16 shows the shape-changing process and the detail of SME of porous scaffold for bone defect.

Subsequently, Senatov et al. [65] conducted a related biological experiment on the PLA/HA porous scaffold as shown in Figure 17(a) and (b), respectively. Cell culture experiments showed that MSC could attach quickly on the scaffold. Haematoxylin and eosin stained MSCs were observed by optical microscope to show excellent cell adhesion and form a cell network as shown in Figure 17(c), and anti-CD105-FITC stained cells were determined by immunofluorescence assay as shown in Figure 17(d). The MSC was spread extensively on the scaffold and forms a strong interaction with the scaffold surface. The porous PLA/HA scaffold has excellent adhesion to MSC, supporting cell survival while stimulating cell proliferation. This is a key prerequisite for its clinical applications. The presence of MSCs in the stent facilitates vessel formation at the site of implantation. This shape memory scaffold, which supports MSC growth and proliferation, has great prospects in the application of bone replacement adaptive implants.

Zhang et al. [24] fabricated the structure of PLA filaments and PLA/Fe₃O₄ composite filaments triggered by magnetic fields through FDM 4D printing. The shape memory structure is triggered by a 27.5 kHz magnetic field and can recover its original shape in a few seconds. The reaction temperature is close to human body temperature which is

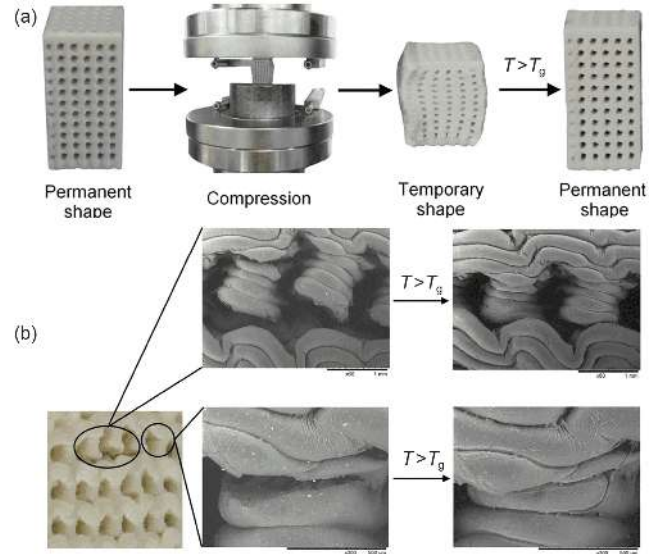


Figure 16 (Color online) (a) Temporary shape of the fixed PLA/HAP porous scaffold by compression, returning to the original shape after heating; (b) "self-healing" of porous PLA/HA scaffold by narrowing the cracks after heating over T_g [64].

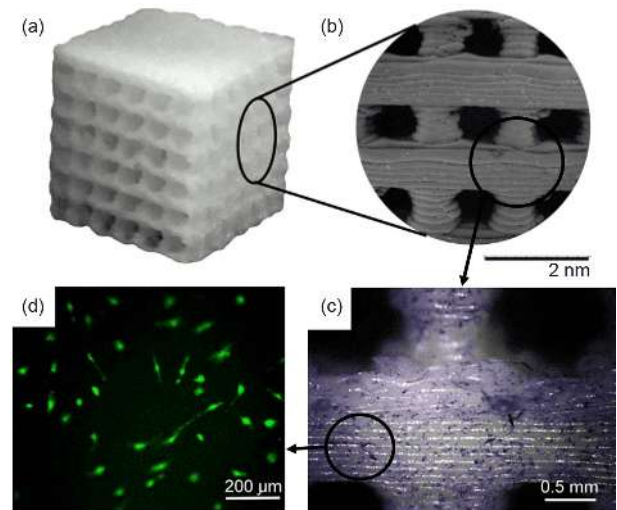


Figure 17 (Color online) (a) PLA/HA porous scaffold; (b) detail of scaffold structure; (c) MSC on the surface of PLA/HA scaffold, optical microscope; (d) immunofluorescence measurement [65].

suitable for biomedical applications. After the structure is implanted in the body, this structure can be driven by a magnetic field and remotely controlled outside the human body. This technology has great potential in medical treatment. Figure 18 shows the shape memory recovery process of the structure, could be applied to the repair of bone tissue, can be designed according to different clinical cases, and has great application potential.

3.4 Tracheal stents

The tracheal stent is a medical device used to repair tracheal

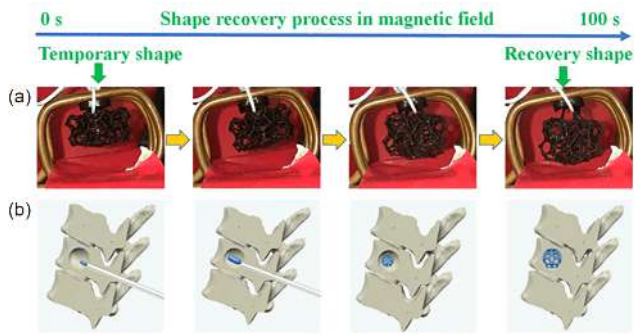


Figure 18 (Color online) (a) Shape recovery behavior of 4D printed composite structure in magnetic field; (b) a simulation showing the mechanism of the 4D structure as a bone repair tool [24].

stenosis or tracheal injury. Most of the clinical cases use non-degradable tracheal stents. With the deepening of research and development of biodegradable materials, degradable tracheal stents have been studied. Some researchers have demonstrated the feasibility of 4D printed tracheal stents, laying the foundation for formal clinical application in the later stages. The degradable tracheal stent can provide mechanical support to the tracheal wall at the initial stage of implantation. As the cell tissue adheres to the stent, it will gradually degrade and be excreted, avoiding the pain of the secondary surgery.

Morrison et al. [54] prepared a kind of tracheal stent with polycaprolactone (PCL) as a printing material using SLA 3D printing technology. It was successfully applied to treat severe tracheobronchomalacia. According to the patient's CT

scan image and digital imaging and communications in medicine, the 3D tracheal model was constructed, and the stereoscopic graphics in the STL format were designed as shown in Figure 19(a), then the simulation combination of the trachea and the stent model was performed as shown in Figure 19(b). It was surgically implanted, and three patients were cured. *In vivo* testing after implantation of the tracheal stent showed that the tracheal stent can be biodegraded by the human body as the time past. They also offer personalized custom designs for patients under the age of one. It not only satisfies the patient's individual requirements, but also can biodegrade the material when the patient's tracheal grows is healthy after 3 years, eliminating the pain of the patient needing multiple operations. A tracheal stent with SME prepared by using 3D printed SMP materials has emerged.

Zarek et al. [51] used a 10000 g/mol methacrylated polycaprolactone as a printing material and successfully printed a shape memory tracheal stent that was deformed by heating using a UV-LED stereotactic printer as shown in Figure 20(a). And related *in vivo* tests were carried out. *In vivo* simulation tests have shown that the tracheal stent can better adapt to the arcade structure and organ cartilaginous ring and provide a stable structure to prevent tracheal occlusion. This tracheal stent can be directly implanted into the body, as *in vivo* follow-up examinations have shown that the tracheal stent can expand with a local increase in temperature until the shape is completely conformable and then the trachea does not change as shown in Figure 20(b). A tracheal stent prepared by 4D printed SMPs can be used to prepare a "private customized stent" according to the individual condition of

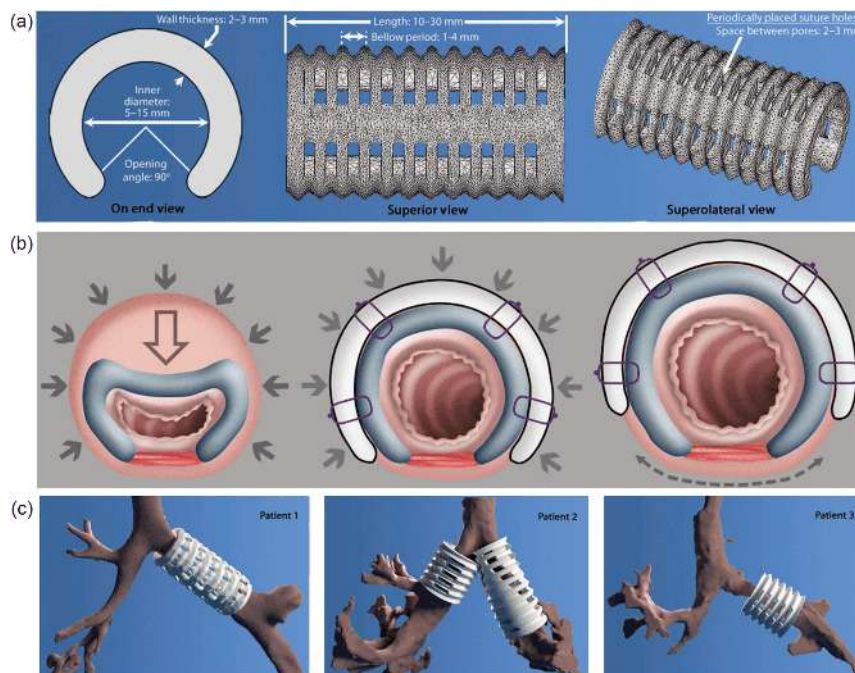


Figure 19 (Color online) (a) STL stereogram; (b) mechanism of tracheal stent in biomedical; (c) virtual assessment over segmented primary airway model for patients [54].

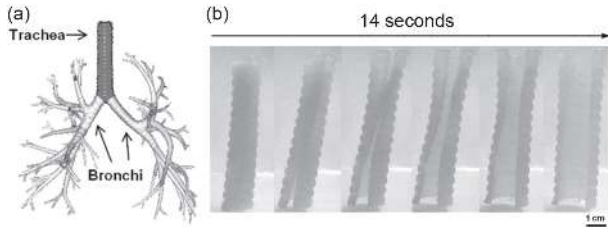


Figure 20 (a) Digital model of trachea and bronchial tree established by MRI scan; (b) shape memory tracheal stent deformation process from temporary shape to final shape within 14 s [51].

the patient's trachea. This solves the problem that the traditional tracheal stent cannot completely conform to the patient's tracheal wall due to individual differences, and the tracheal stent does not need to be fixed to the tracheal wall by surgical traction, but directly achieves the effect of supporting the trachea through its own deformation. Although Liu et al. [61] prepared a tracheal stent, and Zarek et al. [51] did not perform the relevant *in vivo* experiments, the tracheal stent achieved the purpose of supporting the trachea through its own shape change.

Using the shape memory PLA/Fe₃O₄ composite filament as a printing material, and FDM 4D printer, Zhao et al. [55] printed the bioinspired tracheal stent based on a porous glass sponge, as shown in Figure 21(a) and (b). The stent can be implanted in the body while maintaining a temporary shape. Being exposed to an alternating magnetic field, the stent can recover a conformed shape and support the specified position of the trachea as shown in Figure 21(c). The structure is divided into two types, and the bidirectional spiral ridges on the outer wall are designed similar to the glass sponge. This bioinspired shape memory tracheal stent provides a matched supporting and fixation for the trachea.

3.5 Cardiac stents

As an effective means of treating arteriosclerosis, cardiac

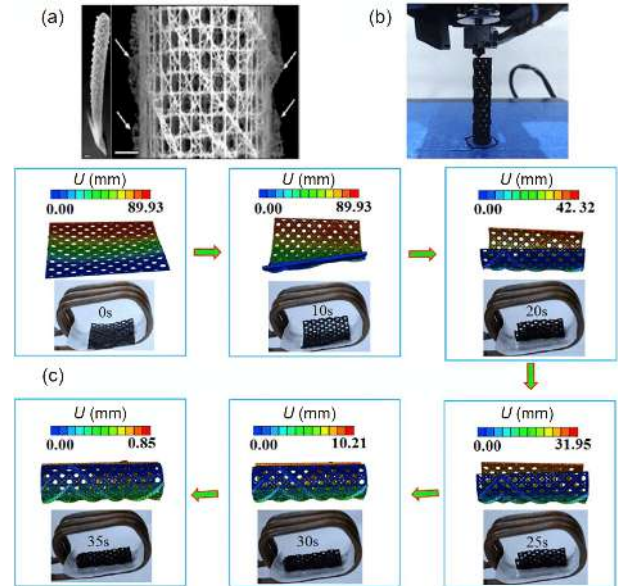


Figure 21 (Color online) (a) Photograph of the entire skeleton of a glass sponge and the fragment of the cage structure; (b) 4D printing of bioinspired tracheal scaffold; (c) shape recovery process of bioinspired tracheal scaffold BTS-I *in vitro* actuated by magnetic field [55].

stents have been used more and more in recent years. Cabrera et al. [66] prepared a stent that can be used in heart valve remodeling surgery by FDM combined with medical technology. The stent can be implanted into the heart by minimally invasive implantation. The stent was placed in the crimping device (Figure 22(a)) before implantation to reduce its diameter to 10 mm (Figure 22(b)), and then transfer the stent from the crimping device to the implant tool with a diameter of 12 mm. (Figure 22(c)). The crimped stent was placed in a 37°C water bath to simulate the heart environment of the delivery stent. The stent was gradually pushed out of the implant tool holder, and automatically expanded into the designed shape (Figure 22(d)–(h)). This stent has a mesh structure that can be reduced to a certain extent and

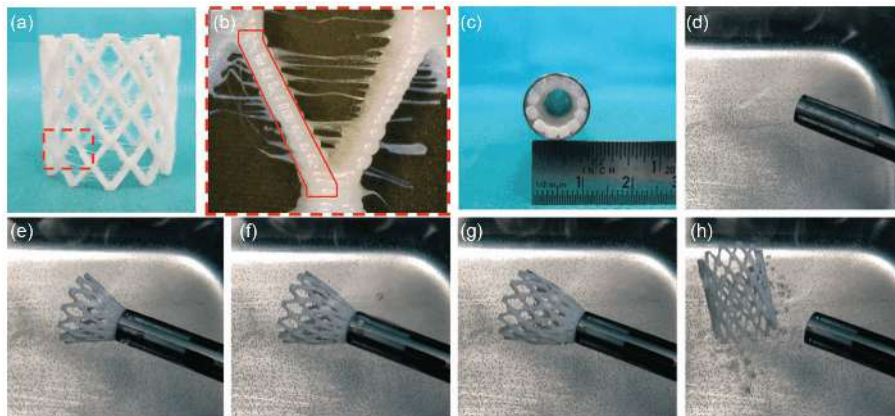


Figure 22 (Color online) An *in vitro* simulated implantation procedure for remodeling a surgical stent in a heart valve. (a), (b) 3D printed polymer stent; (c) the stent is transferred to an internal diameter of 12 mm; (d)–(h) self-expansion process when the stent is pushed out of the system in a 37°C water bath [66].

expands after implantation to automatically restore to its original shape, suitable for pediatric patients. Mechanical performance tests have shown that its mechanical properties are similar to that of normal heart valve Nitinol stents in animal implantation testing. *In vitro* degradation characterization experiments show that the scaffold can also be biodegraded. The shape memory cardiac stent prepared by 4D printing technology will be well used in biomedical area.

3.6 Occlusion devices

Atrial septal defect (ASD) is a common congenital heart disease. Implantable occluder is an effective method to treat structural heart disease. The cardiac occluder is a self-expanding double umbrella structure placed on the heart defect site to seal the defect. Lin et al. [67] 4D printed the shape memory occluders with double-disc shape using PLA/Fe₃O₄ composite filaments. The schematic diagram of ASD and implantation process of the occluder with thin occluding membranes is shown in Figure 23(a). The cardiac occlude device with different numbers of arms is designed and printed as shown in Figure 23(b) and (c). The personalized occlude can be remotely controlled by magnetic field. The SMP occluder that can be customized, biodegradable and remotely driven by combining the programmable SMPs with 3D printing technology, which is expected to become a potential alternative device for metal occluder.

4 Application prospects and development direction

4D printed SMPs and their structures have broad application prospects in various fields. Table 1 summarizes the application prospects of 4D printed SMP in the field of biomedical science. Lu et al. [68] from Xi'an Jiaotong University in China proposed to combine ion-exchange polymer metal composite, dielectric elastomer, SMP and other smart materials with 4D printing technology. A multi-degree of freedom operating arm is available for use in minimally invasive surgical instruments. Shaffer et al. [69] of the University of Texas at Dallas used the post-radiation cross-linked PLA for FDM 4D printed of structure, which has great application prospects in the development of medical devices. Ge et al. [70] using 4D printing research a temperature-sensitive SMP based on the mixture of this SMP and other material. The printed temperature stimuli structure can be recovered from the temporary shape to the initial shape according to the design. It has great potential for use in medical devices and organ scaffolds. Sydney Gladman et al. [58] from the Massachusetts Institute of Technology used a copolymerized hydrogel of cellulose and acrylamide as a printed material, programmed by computer based on the shape of the human body, using 4D printing technology, to print a medical implantable biomimetic organ model. After the biomimetic organ model is implanted into the human body, a part of the

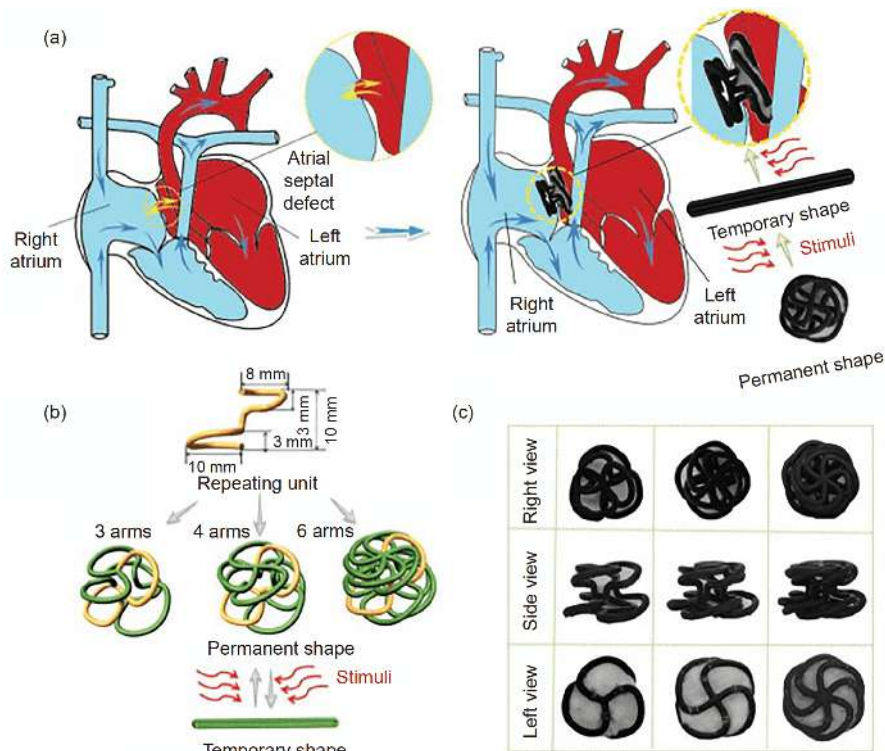


Figure 23 (Color online) (a) Schematic illustration of the ASD prototype before and after interventional therapy with an occluder; (b) schematic illustration of the design of three types of occlude frames with different arms; (c) 4D printed occluders with frame and membranes [67].

Table 1 Application prospects of 4D printing SMPs in biomedical field

Biomedical application prospects	Material	Printing method	T_g	Refs.
Cell scaffold	SOEA	SLA	~20°C	[47]
	Shape memory TPU	FDM	~32°C	[48]
	Castor oil/polycaprolactone triol/hexamethylene diisocyanate thermosetting SMP system	FDM	-8°C–35°C	[49]
	PU	DIW	25°C–37°C	[50]
	Nano-fibrillated cellulose reinforced SOEA	SLA	20°C	[51]
Vascular stent	α,ω -polytetrahydrofuranether-diacrylate	SLA	38°C	[52]
	SMP system after PLA/BP/Fe ₃ O ₄ cross-linking	DW	66°C	[23]
	Polyurethane diacrylate and semi-crystalline polymer	DW	1.5°C	[62]
	PLA	FDM	65°C	[53]
	pNIPAM and pAAM	DIW	35°C	[63]
	PLMC	DIW	37.8°C–50°C	[36]
Bone scaffold	Thermoplastic HA/PLA shape memory composite	FDM	57.1°C	[64,66]
	PLA filaments and PLA/Fe ₃ O ₄ filaments	FDM	~40°C	[24]
Tracheal stent	PCL	SLA	–	[54]
	Methacrylated polycaprolactone	SLA	37°C	[51]
Occlusion devices	PLA/Fe ₃ O ₄	FDM	65°C–67°C	[67]
Medical equipment	Polyurethane diacrylate and semi-crystalline polymer	DW	1.5°C	[62]
	TAIC/PLA radiation cross-linking SMP	FDM	60°C–65°C	[66]
	Photocuring methacrylate	–	~82°C	[68]

components will be degraded by the human body, and the human tissue will grow inward to form a new tissue or organ, thereby exerting the function of the original organ. The research group continues to use this material and has created a new heart stent using 4D printing technology. This heart stent is injected intravenously through the blood circulation system to the designated location of the heart and then self-assembled into a vascular stent. 4D printing combines materials science and medicine science more closely, which is a perfect embodiment of the combination of medicine science and engineering in modern scientific research and will play a more important role in the future development of biomedical field.

It is obvious that 4D printed SMP has broad application prospects in the field of biomedical science. However, biomedical requirements for medical devices and related structures are high, and there are still many problems between the research and the actual application. Therefore, the production and clinical use of 4D printed SMP still need to solve the following problems.

It is necessary to improve the 4D printing technology. There are problems such as long printing time, unsuitable between material types and printers, and precision of the printer. The corresponding technology needs to be further improved. In order to research and develop more high-precision medical devices, the above problems must be solved in the field of 4D printing technology. Research and development of 4D printing technology for biomedical field is one

of the development directions of 4D printing.

In addition, there are many types of SMPs available today, but there are very few shape memory materials that are really suitable for biomedical applications. First, the body is unable to withstand the high T_g of SMP. Second, the mechanical strength of some SMPs does not meet the strength requirements of medical devices. Finally, SMPs used in implanted medical devices are required to be biodegradable and biocompatible. Currently, there are a few types of SMPs for biomedical applications. The development of new materials with lower T_g , good biodegradability and good biocompatibility for the biomedical field to match 4D printing technology is undoubtedly one of the next development directions.

Moreover, easy and rapid response actuation methods are important in biomedical applications. SMP can be triggered by thermal-, electric-, optical-, magnetic- and pH-. And most of the actuate methods for biomedical applications are limited to thermal stimuli. Therefore, there is a requirement to develop multi-stimulus response SMP composites. In the future, the driving method of SMP will inevitably find more breakthroughs in the application of 4D printed magnetic stimuli and pH stimuli shape memory structures to achieve remote actuated control, in order to achieve biomedical application requirements [23,24].

Furthermore, almost all structural components of 4D printed SMP remain at the stage where the finished product has been printed and no biological experiments have been

carried out. Although many SMPs have been proven to be non-toxic in cytotoxicity tests, the long-term study of clinical trials is indispensable for the safety and effective application of 4D printed structures *in vivo*. The research of 4D printed structures in the field of biomedical science still stays in the initial stage of the laboratory. There are still many challenges between clinical application and experimental stage.

5 Summary and outlook

This article describes the development of SMP and 4D printing technologies and introduced the research progress of 4D printed SMP in biomedical field, including vascular stents, tracheal stents, cell scaffolds, bone scaffolds, cardiac stents, occlusion devices and other application prospects. The problems and future development directions of 4D printed SMP in the field of biomedical are pointed out. The application of 4D printed SMP in biomedical field has broken the technical plateau of traditional medical devices, bringing more possibilities for clinical minimally invasive surgery, reducing the number of operations, slow release of drugs, and replacement of tissues and organs. And 4D printed SMP can quickly and accurately provide medical services according to the patient's personal situation, provide patients with personalized customized treatment plan, reduce patient suffering and improve the quality of life. 4D printed SMP provides a new direction for the future of biomedical area. As more and more new shape memory materials for bioprinting have been successfully developed, 4D printers are being developed, and more personalized smart medical devices will be used in the future biomedical area, the combination of 4D printed SMP and biomedical field is a new trend in the future biomedical field.

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