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4D printed hydrogels: fabrication, materials and applications

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Abstract

Four dimensional (4D) printed objects are three dimensional (3D) printed structures whose shape, property, and functionality are able to self-transform when exposed to a predetermined stimulus. The emerging field of 4D printing has attracted wide interest from both academia and industry since first introduced in 2013. Stimuli-responsive hydrogels have become a competitive and versatile group of materials for 4D printed devices due to their good deformability, promising biocompatibility, simple manufacturing, and low cost. This review aims to provide a summary of the current progress of hydrogel-based 4D printed objects and devices based on their fabrication techniques, materials, and applications. The review includes

three parts: the characteristics of different additive manufacturing methods such as direct ink writing, fused deposition modeling, and stereolithography; the properties of various stimuli-responsive hydrogels such as poly(N-isopropylacrylamide) and poly(N,N-dimethylacrylamide), alginate; and diverse applications of 4D-printed hydrogels such as actuators, cellular scaffolds, and drug release devices. Opportunities and challenges for 4D printed hydrogels are discussed and prospects for future development are elaborated.

1. Introduction

In 2013, the concept of 4D printing was first raised by Tibbits as “3D plus time as the fourth dimension.”^[1] Over time, 4D printing has come to be generally defined as the 3D printing of structures whose shape, property, and functionality are able to self-transform when exposed to a predetermined stimulus, such as moisture,^[2] heat,^[3] pH,^[4] and light.^[5] Compared with conventional 3D printed devices, the 4D printed device is able to interact with the environment by responding to stimuli with different output signals such as mechanical motions and biological responses. Therefore, 4D printing techniques have attracted enormous interest in academia and industry.

3D printing, or the additive manufacturing (AM) technique, is the foundation of 4D printing and has grown into a versatile and powerful technology. State-of-the-art 3D printing technology provides fully customized designs of objects with good precision (up to microscale printing accuracy), lower cost, less system complexity and more complicated 3D structure than traditional manufacturing methodologies.^[6] According to ISO/ASTM standards, there are seven main categories of AM technologies, namely, material extrusion, material jetting, powder bed fusion, binder jetting, vat photopolymerization, sheet lamination, and directed energy deposition.^[7-8] **Table 1** summarizes the pros and cons of the seven 3D printing categories. The most extensively used category is the material extrusion method, such as direct ink writing

(DIW) and fused deposition modeling (FDM).^[9-11] In material extrusion, the filament materials are extruded through a nozzle onto the printing platform.^[12-13] As a variety of polymers are thermoplastic or curable after being extruded on substrates, the material extrusion technique has become one of the most popular methods for polymer 3D printing. Another popular method for polymer 3D printing is so-called vat photopolymerization, such as stereolithography (SLA) and digital light processing (DLP).^[12, 14-16] Vat photopolymerization is the technique that was specially designed for the AM of polymer-based materials. During the printing process, it utilizes a light source (usually UV light) to induce photocuring of the liquid monomers. Other than conventional vat photopolymerization techniques such as SLA or DLP, continuous liquid interface production (CLIP), two-photon (2PP) and multiphoton polymerization (MPP) are used to improve vat polymerization methods with enhancement in the speed or resolution of 3D printing.^[17-18] Powder bed fusion such as laser sintering (LS) uses a laser beam to sinter or fuse a thin layer of powders.^[19-20] Currently, the raw materials employed for LS are mainly metal powders such as stainless steel, titanium, and aluminum. Material jetting deposits droplets of the build and support materials onto the platform,^[21] while binder jetting fuses the powder materials with a liquid bonding agent.^[22-23] As for sheet lamination, sheets of engineering materials such as metals and composites are bonded together by heating or pressure to form an object.^[24-26] Directed energy deposition utilizes focused thermal energy to melt and fuse the raw materials.^[27-29] During these processes, melted, liquid, or sheet materials are physically or chemically bonded to form the 3D objects.

While a wide range of smart materials have been utilized for 4D printing, polymers that include hydrogels have attracted much attention due to their large deformability, good flexibility, and lower cost compared to metals and ceramics.^[30-32] Hydrogels are three-dimensional crosslinked polymer networks with large amounts of water. The crosslinks can be chemical (covalent bonding) or physical (such as van der Waals forces, electrostatic interactions, and hydrogen-bonds), enabling the structural integrity of the hydrogel networks to be maintained with

significant water content.^[33-34] Compared with conventional polymer materials, hydrogels have the unique advantage of softness, biocompatibility, and multifunctionality due to their large water content,^[35] resulting in wide biomedical applications such as drug delivery systems,^[36-37] implants,^[38] contact lenses,^[39] cellular scaffolds,^[40] and cell cultures.^[41] The stimuli-responsive hydrogel is a unique type of hydrogel having the ability to sense changes in temperature, pH, light, or other environmental factors, exhibiting responses via changing shape, color, mechanical properties, or biological properties.^[42-43] Because of their ability to smartly respond to the ambient environment, stimuli-responsive hydrogels have become a competitive candidate for 4D printing. Some intensively researched stimuli-response hydrogels include poly(N-isopropylacrylamide) (PNIPAm),^[44-45] poly(N,N-dimethylacrylamide) (PDMAAm),^[46] alginate,^[47] hyaluronic acid^[48] and gelatin.^[49] Although there is much literature published on 4D printing polymers and their applications,^[50-51] to the best of our knowledge, there are no reviews specifically dedicated to 4D-printed hydrogels.

This review aims to provide a summary of commonly used AM techniques for hydrogels, the various stimuli-response hydrogels and their applications to 4D printed hydrogel devices (Figure 1). First, various AM techniques are summarized, including DIW, FDM, and SLA (Figure 1). Second, some commonly used stimuli-responsive hydrogels such as PNIPAm, PDMAAm, calcium alginate, agarose, and so forth are discussed according to the type of stimuli they respond to (Figure 1). Moreover, applications of 4D hydrogel smart devices are elaborated upon (Figure 1). Finally, challenges and future trends of 4D printed hydrogels are discussed. The object of this review is to broaden research interests and inspire further innovative ideas for hydrogel-based 4D printing devices and nourish the development of 4D printing techniques.

2. Additive manufacturing technologies for 4D printing

Among the seven categories of additive manufacturing technologies, material extrusion and vat photopolymerization have extensively employed polymeric materials.^[60] In particular, this section reviews the 3D printing methods that are most amenable to smart polymers such as hydrogels, including direct ink writing, fused deposition modeling, and stereolithography.^[51] The readers are also referred to relevant reviews on other 3D printing processes.^[60-62]

2.1. Direct ink writing (DIW)

DIW is one of the most common extrusion-based AM processes providing excellent interfacial bonding and tunable mechanical properties. Typically, viscoelastic polymer inks are extruded through a nozzle onto a build stage line-by-line and layer-by-layer.^[51] Proper rheological properties such as shear-thinning are necessary to fulfill the requirement of extrusion. With viscosity decreasing under increasing shear stress during extrusion, the ink can flow like a liquid without excessively high internal pressure. In addition, the printed materials should be stabilized for the final structure, which can be achieved through several approaches. UV curing is one of the commonly used approaches to stabilize the printed products. Wei and co-workers utilized the DIW technique to print UV crosslinking poly(lactic acid) (PLA)-based 4D architectures that could be thermally or remotely actuated by adding Fe₃O₄ nanoparticles.^[52] As shown in **Figure 2a**, the ink, consisting of PLA dissolved in dichloromethane, was extruded through the syringe micronozzle. After extrusion, the solvent evaporated, and UV irradiation was used to crosslink the polymer. As a result, the ink rapidly transitioned from liquid to solid, which was necessary for filament fabrication. Figure 2b shows a complex shape fabricated by this DIW method with a length of 12.8 mm and diameter of 2.4 mm. A thermo-responsive 4D flower-like structure was subsequently fabricated through this approach (Figure 2c). At the initial state, the device was a flower-like shape. When heated above its glass transition temperature (T_g , 74.5 °C for PLA), the structures became flexible and could be deformed to a

circular temporary shape. The temporary shape of the deformed device could be fixed by rapid cooling below T_g and could be recovered back to the initial shape when reheated above the T_g . In addition, adding Fe_3O_4 nanoparticles to PLA during the printing process increased the mechanical properties and shaped recovery capability of the materials, and also introduced a magnetic response to the 4D printed structures. As shown in Figure 2d, the deformed nanocomposite cylinder recovered its original shape by remote actuation of the alternating magnetic field. Liu et al. fabricated 4D printed tubes consisting of PNIPAm and polyacrylamide (PAAm) hydrogel through the UV photopolymerization technique.^[63] Figure 2e shows the scheme of the 4D printing process: The NIPAm ink (designated as “Active Ink”) and AAm ink (designated as “Passive ink”) were contained in two separate nozzles and extruded at the same time to form the alternating vertical segments in the tubular structure. Subsequently, the tube was polymerized by UV light. As shown in Figure 2f, when immersed in DI water at 50 °C, the structure kept its tubular shape. When the water temperature was decreased to 25 °C, the tubes deformed into a structure through buckling in order to relieve the compressive axial stresses resulting from the different swelling behavior of active PNIPAAm segments and passive PAAm segments.

Adding a rheology modifier into the ink is another approach to improve the stability of the final structure. Chen et al. demonstrated the effect of carbomer as the rheology modifier for DIW of various types of hydrogels.^[6] Carbomer can enable the ink to undergo a fast sol-gel transition once forced out from the nozzle, and increase the viscosity, yield stress, and other mechanical properties of the ink. For example, the PAAm-carbomer hydrogel had an improved Young’s modulus of 40 kPa compared with pure PAAm (17 kPa). By introducing ferromagnetic nanoparticles to the AAm-carbomer ink, Chen et. al printed a magnetic hydrogel octopus that could be remotely actuated by the magnetic field placed below it and could “swim” across the petri dish (Figure 2g, 2h).^[6] Such devices could be used for soft robotics and biomedicine.

2.2. Fused deposition modeling (FDM)

Another widely used extrusion-based AM technology is fused deposition modeling (FDM), also called fused filament fabrication (FFF). Different from DIW, FDM heats the solid filaments in the nozzle and the materials soften for extrusion (Figure 3a). Thermoplastics, which are not covalently crosslinked, are ideal polymers for FDM as they melt upon heating and re-solidify when cooled.^[51] Zhang et al. used a commercial FDM polymer printer to fabricate PLA strips that could be thermally actuated to undergo pattern transformation.^[64] The PLA polymer was first heated in the nozzle and extruded onto the platform followed by rapid cooling below its T_g . Thus, the solidified pattern could retain its structure after removal from the platform. When reheated above T_g , the internal stress or strain accumulated in the material due to the constraint of the platform and existing strips during printing was released, resulting in the pattern transformation. As shown in Figure 3b and 3c, when heated up to 90 °C, the circular rings in the hexagonal lattice transformed into hexagons, and those in the square lattices transformed into quadrangles spontaneously. Similarly, Zhang and co-workers printed PLA strips on a thin sheet to fabricate thermo-actuated self-folding structures.^[65] When heated up to 105 °C, the release of internal strain was counteracted by the mismatching of the different coefficients of thermal expansion (CTE) of PLA and the paper sheet; thus, the composite petals remained flat. However, after cooling, the composite sheet self-folded into a flower-like structure, which could recover to a flat shape when reheated (Figure 3d). A variety of 4D lightweight architectures such as helical structures and orthogonal periodic structures were also fabricated from the composite sheet. As FDM technology does not require UV exposure, it can be used for fabrication of photo-responsive structures. Yang et al. fabricated a photo-responsive cubic frame by FDM through a layer-by-layer deposition.^[66] The printed material consisted of polyurethane (PU) as the shape memory polymer and carbon black (CB) as the photothermal conversion material. As shown in Figure 3e, the cubic frame deformed to a temporary shape

that could recover its original shape with illumination by a light source or sunshine. The time required for shape recovery was reported to decrease with increasing light intensity. This composite material was also used to print the petals of a sunflower (Figure 3f). Under light illumination, the carbon black particles converted absorbed light to heat, increasing the temperature above the T_g of the polymer. Therefore, the sunflower bloomed when recovering from its temporary shape, recovered by external force to its original shape. The above-mentioned facile printing strategies can open a new avenue to fabrication of soft robotics, mechanical metamaterials, and tissue engineering structures or devices.

2.3. Stereolithography (SLA)

As one of the vat polymerization AM processes, SLA has advantages including high spatial resolution and high fabrication speed. It uses photo-polymerizable materials such as acrylates and methacrylamides as the polymer resin, which is cured by a light source to form the designed 3D structures layer-by-layer. ^[67] There are several configurations of SLA depending on the orientation of the light source. As shown in Figure 4a, the build surface in the “upside-down” configuration is placed above a comparatively shallow resin vat that has a transparent window in its base. The light is irradiated on the building surface through the transparent window, and the thickness of each layer depends on the distance between the building surface and the transparent window. Once a layer is fully printed, the build surface moves upward, and the next layer will be printed. On the other hand, for the “right-side-up” configuration, the build surface is submerged in a vat of liquid resin, and the thickness of the printed layer is equal to the submerged depth of the build surface. In this type of configuration, the light source is above the build surface and selectively cures the precursor by light irradiation. Once the layer is fully cured, the build surface descends deeper into the precursor for the printing of the next layer. Zarek et al. employed the “upside-down” SLA technique to fabricate polycaprolactone (PCL)-

based shape-memory structures.^[68] The printing platform descended into the vat of molten methacrylated PCL oligomers for the printing of PCL thin layer; then the printing platform moved upward to print another layer.

The conventional SLA uses a laser beam as the light source. However, if a projector is used as the light source instead of a laser beam, the system is referred to as digital light processing (DLP). Because the projection of a digital image enables the entire pattern of each layer to be cured in one exposure, the printing and production speed of the DLP process is much faster than the conventional SLA technique.^[69] Zhao et al. printed poly(ethylene glycol)diacrylate (PEGDA)-based, environmentally responsive self-folding origami structures using DLP methods.^[70] By controlling the light intensity, the degree of crosslinking within the thin sheet of polymer was different, resulting in shape bending when the uncured oligomers were desolvated from the network. As shown in Figure 4b, the as-cured device showed a flattened six-petal flower shape. During the UV curing, the first grayscale pattern (the “1st” pattern shown in Figure 4b), followed by the second grayscale pattern (the “2nd” pattern shown in Figure 4b), was projected to the printed resin from top and bottom layers, respectively. Because the light intensity of the grayscale ranged from weakest in black regions to strongest in white regions, the parts designed for panels were fully cured, while the remainder of the parts were relatively slightly crosslinked to form hinges that could bend after desolvation. As a result, when the solvent (acetone) in the structure was fully desolvated by submerging the structure in water for 1 h, self-folding happened, resulting in a folded structure. If the folded structure was submerged in acetone, it would swell and reverse back to its original shape. Ge et al. used a high-resolution DLP method called projection micro-stereolithography (PμSL) to fabricate multi-material-shaped memory objects consisting of various methacrylate-based copolymers.^[71] As shown in Figure 4c, a computer-aided design (CAD) model was first sliced into a series of closely spaced horizontal two-dimensional (2D) digital images, which were transmitted to a digital micro display, working as dynamic photo-masks to control the areas of the material exposed to UV

irradiation. Once one layer of material was solidified, the substrate was lowered by the elevator, followed by projection of the next image to polymerize a new layer on top of the preceding one. For each layer, multi-material fabrication was enabled by automatic material exchanging. By pre-shaping the flower above its T_g , the co-polymer was able to achieve a programmable shape memory effect. As shown in Figure 4d, the co-polymer- made flower could be programmed to either open or close upon heating. By applying the same idea, the grabbing and releasing functionality of grippers could also be achieved (Figure 4e).

3. Stimuli-responsive hydrogels

In this section, different stimuli-responsive hydrogels are reviewed. Their stimuli-response mechanisms, properties, and the fabricated devices are summarized. It is worth mentioning that the printability of the hydrogel is an important factor affecting the selection of the fabrication technique and the quality of the final product. For example, the extrusion-based methods such as DIW and FDM require the material to be shear-thinning and have an adequate yield strength. On the other hand, for the SLA method, an ideal candidate material should be transparent in order to allow light to pass through and cure the materials. Meanwhile, the material should have a low viscosity so that the polymer resin can be adequate for sequential printing.

3.1. Moisture-responsive hydrogels

Hydrogels are well-known for their significant water content and the ability to absorb a large amount of water or biological fluids. Upon dehydration, hydrogels usually shrink in volume due to the loss of small water molecules. Such swelling and de-swelling behaviors in response to the change in environmental humidity have been utilized to fabricate responsive hydrogel 4D structures. Cao et al. fabricated 4D configurable hygroscopic robots with a co-polymer

between crystalline poly(ethylene glycol) (PEG) and poly(tetramethylene glycol) (PTMG).^[72] As shown in Figure 5a, the hygroscopic actuator consisted of a moisture-sensitive layer (namely, an “active layer,” the yellow layer in Figure 5a) made from the PEG-PTMG co-polymer and an inactive layer made from beeswax (the thin black layer in Figure 5a). During the humidification and dehumidification processes, the formation and dissociation of the hydrogen bonds in the co-polymer led to a fast-hygroscopic expansion of the co-polymer. As a result, the actuator bent toward the inactive layer side. Figure 5b shows a 4D aircraft model with the hygroscopic responsive actuator as the wing material. The wings of the aircraft model showed reversible flapping motions with the humidity changing between 20% and 80%. With a similar actuating mechanism, cellulose-hydrogel composite ink was printed by Mulakkal et al. to fabricate a shape memory petal.^[73] Cotton derived pulp fibers were uniformly dispersed in the sodium carboxymethyl cellulose (CMC) to enable additive printing via extrusion. At the base of the composite petals, there was an additional circular layer of CMC/hydroxyethyl cellulose (HEC) hydrogel without pulp fibers. The difference between the swelling ratios of these two materials enabled out-of-plane morphing when dehydrated. As displayed in Figure 5c, the 4D petal structure, after crosslinking, reverted to a flat shape upon hydration at room temperature and could be recovered by drying the specimen in air.

Other than employing swelling differences between two types of material, Gladman et al. developed an anisotropic swelling hydrogel composite with a soft N, N-dimethylacrylamide-based matrix and stiff nano-fibrillated cellulose (NFC).^[74] As the cellulose fibrils were aligned along the printing path due to the shear stress/strain during printing, anisotropic stiffness in the printed filament was introduced. As a result, the responsive behavior would be observed in the longitudinal and transverse direction. The flat bilayer structure fabricated by such filaments would change to a curved shape after swelling. Following the concept of asymmetric swelling, Ji et al. printed polyethylene glycol diacrylate (PEG400DA)/2-hydroxyethyl methacrylate (HEMA)-based hydrogel structures with the anisotropic swelling property.^[75] During the

printing process, the grooves were printed on one side of the printed strip to guide their shape-changing process, and the orientation of the grooves governed the direction of the asymmetrical swelling direction (Figure 5d). Figure 5e shows that the strip with perpendicular grooves spontaneously bent to a circle when subjected to swelling in water, while the inclined grooves caused the strip to twist and form a helical shape in Figure 5f. After being removed from water and placed in air, the samples gradually recovered their initial shape.

Liang and co-workers achieved controllable deformations triggered by dehydration using alginate-based hydrogel microfibers with embedded asymmetric gas bubbles.^[76] A microfluidic coaxial device was used to inject monodispersed bubbles with different patterns (Figure 5g). The gas was first pumped into an alginate solution (named the “middle fluid” in Figure 5g) and formed the bubbles inside. As the alginate solution was injected into the CaCl_2 solution (named the “outer fluid” in Figure 5g) through the transition tube, the gas bubbles flowed together with the alginate solution and contacted the CaCl_2 solution. Because the alginate crosslinked with the calcium ions to form a hydrogel, the gas bubbles would be trapped in the hydrogel giving a porous structure. Generally, the bubbles would not stay at the center of the fiber. Instead, they would deviate to one side (namely, the “air side” in Figure 5g) due to the buoyancy force of the bubbles. The bubble pattern could be controlled by tuning the flow rate of the gas and the middle flow rate. Figure 5h shows the 3D butterfly-like structure fabricated by the asymmetrical bubble hydrogel microfibers, which displays the capability of the fabricating 3D structure through the microfluidic technique. Figure 5i shows the synthesized alginate hydrogel fiber with the bubble trapped. It could be observed that the bubble was of a similar size and distributed evenly through the fiber. Moreover, instead of staying at the center of the fiber, the bubbles deviated to, and gave a thinner wall on, the air side (side view of the inverted microscope in Figure 5h). Subsequently, the authors found that the bending curvature of the fibers had a linear relationship with the gas flow speed during fabrication (Figure 5j). With the gas flow rate increased from $10\ \mu\text{l}/\text{min}$ to $50\ \mu\text{l}/\text{min}$, the actuation curvature of the fiber increased from less than $0.5\ \text{mm}^{-1}$

to $\sim 1.75 \text{ mm}^{-1}$. The authors then explained that the possible reason for this observation was the asymmetrical shrinkage principle. With the cross-sectional image of fiber (green patterns in Figure 5i) at different gas flow rates, it could be observed that a larger gas flow rate would lead to a larger degree of deviation of the bubbles. As a result, a stronger asymmetrical shrinkage effect was achieved and caused a larger bending curvature of fiber (white fibers in Figure 5i). Meanwhile, the bending could be fully reversed when hydrated. This strategy can also be used to create shape-morphing systems for humidity sensing and soft actuators.

3.2. Thermo-responsive hydrogels

Heat is a widely established stimulus to trigger shape-changing of hydrogels. The temperature-sensitive hydrogels undergo reversible volume change due to the collapse or expansion of polymer chains in the solvent at critical temperatures, the so-called “coil-globule transition.”^[50] PNIPAm is one of the most studied thermo-responsive materials. As showed in Figure 6a, when the temperature of the aqueous solution is above the lower critical solution temperature (LCST) of PNIPAm ($\sim 32^\circ\text{C}$), its polymeric network (black lines in the figure) collapses and expels water, resulting in a decrease in volume. On the other hand, when the temperature is lower than the LCST, the polymer chain expands and the water molecules are within the polymer network.^[77-78] Bakarich et al. designed a thermo-responsive ionic covalent entanglement (ICE) hydrogel composed of PNIPAm and alginate.^[79] In this composite hydrogel, PNIPAm served as the thermal-responsive material, and the role of alginate was to improve the mechanical properties of the hydrogel. A composite, hydrogel-based, thermally controlled microvalve was fabricated (Figure 6b): when submerged into cold water at 20°C , the valve was in an open state and allowed the water to flow through. Once the water temperature (60°C in this case) was above the LCST of PNIPAm ($\sim 32^\circ\text{C}$), the six parallel strips made from alginate/PNIPAAm hydrogel would swell and close the gap. The valve would open again if the water temperature

decreased. This group further examined the reaction speed of the valve (Figure 6c). Upon submerging of the valve in a hot water bath (60 °C), the flow rate through the valve was 1.4 ml s⁻¹. After 3.5 minutes, the flow rate decreased and stabilized at ~8 µl s⁻¹. It was concluded that the valve was able to open and close within 3.5 minutes. Similarly, Naficy et al. used PNIPAAm with a thermally nonactive polymer, poly(2-hydroxyethyl methacrylate) (pHEMA), to fabricate shape morphing structures.^[80] The reversible shape transition was achieved by heating and hydration. As shown in Figure 6d, the as-printed bilayer structure had a top layer of PNIPAAm-based hydrogel (the white region in the Figure 6d) and a bottom layer of pHEMA-based hydrogel (the transparent region in Figure 6d). When brought in contact with water at 20 °C, the PNIPAAm-based layer had a higher swollen ratio than the pHEMA-based layer; therefore, the bilayer bent towards the pHEMA side. By increasing temperature to 60 °C, the swelling ratio of the PNIPAAm-based hydrogel decreased dramatically due to the coil-to-globule transition; thus, the bilayer hinge deployed and the actuator bent toward the PNIPAm side. The hybrid bilayer structure was then used to fabricate a cubic box (Figure 6e). The flat bilayer folded to a closed box upon hydration at 20 °C and opened up to its flat state as the temperature rose to 60 °C.

Other than PNIPAm, some hydrogels such as agarose and gelatin exhibit the upper critical solution temperature (UCST) behavior.^[81-82] When the temperature is higher than the UCST of the hydrogel, the hydrogel is in a homogeneous system without any phase separation. However, if the temperature is lower than the UCST temperature, phase separation occurs, and the mechanical and optical properties experience a dramatic change.^[83-84] Guo et al. designed a 4D printing hydrogel fabricated by *in situ* polymerization of agarose and acrylamide.^[85] As shown in Figure 6f, when the temperature was above the UCST of agarose (35 °C), the hydrogel was in a homogeneous phase and could be easily deformed. As the temperature decreased below 35 °C, the extended chains of agarose self-aggregated into a parallel structure, forming nanofibers which, in turn, improved the strength of the composite hydrogel. As a result, the

shape of the hydrogel was fixed. The group printed octopus-like hydrogel to demonstrate the deformation and recovery process (Figure 6g). The printed octopus-like hydrogel was first heated to 95 °C and deformed; it was subsequently rapidly cooled to room temperature in order to fix its shape. Once the deformed octopus was heated back to 95 °C, it recovered its original shape.

3.3. Chemically-responsive hydrogels

Many hydrogels such as alginates,^[86] PAAm,^[87] and poly(acrylic acid) (PAA),^[88] are responsive to changes in chemical environment such as pH or ion concentration. The mechanism of their chemical-stimuli response is due to the crosslinking and dissociation of the polymer chains when interacting with ions.^[89-90] Because the polymer chains in the chemically responsive polymer are mainly linked through electrostatic interactions, the changing of the ion concentration will interfere with the strength of the electrostatic interaction and influence the properties of the hydrogels. Kirillova et al. employed alginate and hyaluronic acid to demonstrate the fabrication of hollow self-folding tubes.^[91] The fabrication process of a hollow self-folding tube is shown in Figure 7a. A methacrylated alginate (AA-MA) or methacrylated hyaluronic acid (HA-MA) precursor with or without cell was extruded on a glass or polystyrene (PS) plate, and the extruded precursor was subsequently polymerized by green light. After immersion of the as-printed objects into water, phosphate-buffered saline (PBS) or cell culture media, the printed hydrogel spontaneously self-folded and formed a tube. The ion-response demonstration of such a hydrogel is shown in Figure 7b. In water, the hydrogel was in the hollow tubular shape. When submerged into CaCl₂, the Ca²⁺ ions crosslinked the AA-MA hydrogel, which prevented it from swelling, and stiffened the film. As a result, the folded tube became unfolded. The unfolded hydrogel could be folded again by submersion into ethylenediaminetetraacetic acid (EDTA) solution. EDTA would remove the Ca²⁺ ion in the AA-

MA hydrogel and the hydrogel would re-fold into a tubular shape. Hydrogels containing a large number of carboxylic groups in the side chains can be responsive to the pH of the liquid environment.

Hu and co-workers reported on the different swelling behaviors of an acrylic acid (AAc)-based hydrogel in alkaline and acid solutions.^[92] As shown in Figure 7c, when the pH value was greater than 9, the carboxylic groups of AAc were ionized by releasing protons, resulting in stronger electrostatic repulsion forces between the carboxylate moieties such that the hydrogel expanded in volume. On the other hand, at lower pH, the decreasing amount of charged carboxylate moieties led to smaller repulsion forces between the molecules, thus the AAc-based hydrogel contracted in the acidic environment. Figure 7d shows the results of the contraction ratio at $\text{pH} < 9$, expansion ratio at $\text{pH} > 9$, and the relative expansion ratio (RER) of a printed cubic plate and a circular plate. At $\text{pH} < 9$, the expansion ratios for the cubic and circular plates were 0.072 and 0.066, respectively. On the other hand, the expansion ratios for the cubic and circular plates were, respectively, 0.53 and 0.52 at $\text{pH} > 9$. Moreover, the RER of the cubic and circular plates was the same (0.43). Therefore, it could be concluded that the expansion of the hydrogel was related to its material but not its shape. The hydrogel was then designed to capture microparticles by controlling the pH value (Figure 7e). After being immersed in an alkaline solution ($\text{pH} > 9$), the cage-like hydrogel structure swelled (stage II in Figure 7e) and allowed the particles to enter into the cage (stage III in Figure 7e). Subsequently, by reducing the pH of the solution, and the cage-like hydrogel contracted to successfully trap the particles inside the cage (stage IV in Figure 7e). By modifying the polymer system so that the ionization pH threshold was reduced to the physiological pH, this technique could be utilized in the field of biomedical engineering such as drug deliveries.^[93] Larush et al. used polymerizable inks that were composed of water, acrylic acid monomer, polyethylene glycol diacrylate as a cross-linker, and a water dispersible photo-initiator composed of nanoparticles of (2,4,6- trimethylbenzoyl-diphenylphosphine oxide (TPO)).^[94] The use of photoinitiator nanoparticles opened the way for

printing objects in water with a high resolution by SLA technologies. The printed structures exhibited a strong pH-responsive swelling, e.g., increase in volume at high pH and shrinkage at low pH. The aim of this study was to develop a responsive drug delivery system that would start to release a loaded drug at pH conditions of the intestine, while not releasing the drug at the acidic conditions of the stomach.

3.4. Other stimuli-responsive hydrogels

Other than the intensively researched moisture- and thermal-responsive hydrogels, hydrogels responding to other types of stimuli have also been reported. McCracken et al. reported a 4D printed soft aquatic actuator (SAA) with magnetic Fe_3O_4 nanoparticles encapsulated within an algae-derived alginate ionic hydrogel as the magnetic responding material.^[95] The SAA was able to move in water in the presence of a magnetic field. When the strength of the magnetic field increased from 400 to 700 Gauss, the movement speed of the SAA increased from 0 to 4 mm s^{-1} (Figure 8a). Similarly, Lee et al. reported on a Fe_3O_4 /Laponite/PDMAAm magnetic field responsive hydrogel (Figure 8b).^[96] Due to the utilization of PDMAAm as the matrix, NIH/3T3 mouse fibroblast cells had an ~80% cell viability when cultured on the nanocomposite surface, which indicated good bio-compatibility. The addition of laponite provided the nanocomposite hydrogel with good mechanical strength (toughness 4198 kJ m^{-3} , Young's modulus 0.035 MPa), which was significantly higher than the pure PDMAAm hydrogel (toughness 162.3 kJ m^{-3} , Young's modulus 0.015 MPa).

Another response trigger, near-infrared (NIR)-induced dehydration, was demonstrated by Luo et al. for shape-morphing of alginate/polydopamine (PDA)-based scaffolds.^[97] Alginate scaffolds were reported to fold upon dehydration, but the process was slow at room temperature. PDA, as a biocompatible material with excellent photothermal effect, could convert absorbed light to heat to rapidly increase the temperature of the scaffold, thus accelerating the

dehydration and shape-changing process. The bending process of alginate/PDA bilayer could be controlled by the power and exposure time of the NIR laser; with an increase of the laser power from 0.3 W cm^{-3} to 1.5 W cm^{-3} , the bending time of the scaffold decreased from 600 s to 180 s, which was due to acceleration by heating. Moreover, the local shape change of the scaffolds could be controlled by printing alginate/PDA struts in the designed area and direction on the biphasic scaffolds. This strategy can be used to fabricate self-folding 4D cell-laden structures in the field of 4D bioprinting of artificial tissues or organs.

Multi-stimuli responsive hydrogels is another important topic as it has a high potential for multi-functional applications. Ma et al. introduced a perylene bisimide-functionalized, hyperbranched polyethyleneimine (PBI-HPEI)-graphene oxide PNIPAm (GO-PNIPAm) hydrogel that responded to both temperature and pH.^[98] At the initial stage, the 4D actuator was wrapped, and the pH-sensitive PBI-HPEI (blue- and yellow-colored layers in Figure 8c) was covered by the thermally sensitive GO-PNIPAm layer (black color in Figure 8c). Because the GO-PNIPAm layer blocked most of the excitation light (532 nm green laser), no fluorescence would be observed at the initial stage (Figure 8c). When the temperature increased, the thermal actuation of the GO-PNIPAm layer was triggered and unwrapped the flower-like device. As a result, the PBI-HPEI was excited by the laser, and weak fluorescence was observed. The intensity of the fluorescence could be tailored by changing the pH. When the pH decreased, the fluorescence would be enhanced. On the contrary, the fluorescence would be diminished with the increase in pH due to the increased photoinduced electron transfer (PET) process between amino groups and PBI fluorophores in alkali conditions.^[99] Figure 8d demonstrates the actual multi-responsive device. When the ambient temperature was 20°C with a pH value of 10, the flower was folded, and no fluorescence was observed. Once the temperature increased from 20 to 40°C , the device gradually unfolded within 480 s, and the fluorescence generated by the PBI-HPEI was observed. Subsequently, the pH value was tuned between 10 and 2; a change of fluorescence intensity was observed. This thermal-, light- and pH-responsive hydrogel actuator

could mimic some natural creatures that could not only could move, but also adjust their body color.

4. Application of 4D printed hydrogel devices

4.1. Actuators

Actuators convert external stimuli into mechanical motion and have been widely applied in nanomechanical systems, micro-robotics, and biomimetics.^[100-101] Stimuli-responsive hydrogels have attracted great attention in the field of actuator applications due to their reversible shape-changing that can be triggered by various external stimuli. Combined with additive manufacturing technologies, a variety of hydrogel actuators have been applied as hinges^[102-103] and valves.^[104-105] Baker et al. fabricated 4D printed origami-inspired structures actuated by localized swelling of hydrogel regions.^[54] As shown in Figure 9a, the trilayer regions were printed to have hydrophobic polyurethane (PU) top and bottom skins (the pink-colored layer in the figure) and a hydrophilic PU core (the white-colored layer in the figure), whereas the bilayer active actuation region only had one side of the skin. Therefore, the bending of this hinge was actuated via different degrees of swelling upon hydration. By designing the orientation and positioning of this bilayer/trilayer hinge structure, various complex geometries could be autonomously folded up. Figure 9b shows the deformation process of a printed trilayered actuator. The actuator was designed to have a series of increasing skin gaps (left to right) in the top surface. In the dry state, the actuator was in a flat shape, and it deformed to form an in-plane spiral structure upon hydration. This 4D printing technology is capable of creating robust and complex origami designs. On the other hand, Hua et al. fabricated a dual-responsive hydrogel actuator based on the PAAm/PAAc complex hydrogel.^[106] The PAAm itself was a non-thermally-activated material. However, when penetrated by the polymer chain of PAAc, the composite showed a UCST property. As a result, the bilayer hand-shape device,

which consisted of the non-active PAAm layer and the PAAm/PAAc layer, actuated within the temperature range of 5 to 60 °C (Figure 9c). Moreover, the researcher observed that the bending angle of the actuator was influenced by the ion present in the immersed solution. For example, the concentration of urea could affect the bending curvature of the actuator through disrupting the hydrogel bond between polymer chains (Figure 9d). With the concentration of urea increased from 0.5 M to 2.0 M, the actuating angle of the actuator increased from 150° to 240°. Furthermore, the bending direction of the actuator could also be controlled by introducing different types of ions into the immersed solution. As shown in Figure 9e, the Cl^- and SCN^- ions would cause a circular actuator to unroll; SO_4^{2-} ion would cause the circular actuator to bend into more than one circle. The ion-responsive ability of the actuator makes the PAAm/PAAc complex hydrogel a candidate for biomedical applications.

The gripper is a special type of actuator. Different from conventional actuators that output simple mechanical motions such as bending, the gripper is able to spontaneously grasp the object upon receiving stimuli.^[107] Because of its softness, deformability, and the ability to absorb shock, the hydrogel-based gripper is suitable to grip soft objects and has broad application in the biomedical field.^[108-110] Shiblee et al. fabricated a gripper made of bilayer structures of shape-memory hydrogels printed by a customized stereolithographic printer.^[59] The bilayer was composed of poly(N, N-dimethyl acrylamide-co-stearyl acrylate) [P(DMAAm-co-SA)]-based hydrogels of various monomer concentrations of hydrophobic crystalline stearyl acrylate (SA). The low SA concentration side (namely, the “SMG90-SA10” side) was the active layer for the actuation. On the other hand, the high SA concentration side (namely, the “SMG70-SA30” side) controlled the stiffness of the bilayer structure and further affected the bending speed of the structure. Figure 10a shows the gripping motion of the gripper made of the bilayer structure. The gripper was first immersed in water at 50 °C (Figure 10a i), and it grasped the bottle after submersion for approximately 30 minutes (Figure 10a ii, iii). By cooling down to 30 °C, which was below the glass transition temperature (T_g) of the hydrogel, the

gripper was able to lift and transport the object in both water and air (Figure 10a iv, v). The releasing process was actuated by heating. When immersed in water of 70 °C, the gripper was able to release the bottle within one minute (Figure 10a vi). The gripper would recover to the flat shape through exposure to air at high temperatures to evaporate the water in the hydrogel. Kobayashi et al. further developed the thermal-responsive hydrogel gripper by introducing the biodegradation function.^[111] The researchers fabricated a bilayer gripper consisting of an active poly(oligoethylene glycol methyl ether methacrylate-bis(2-methacryloyl)oxyethyl disulphide) [P(OEGMA-DSDMA)] layer, and a non-swellable poly(acrylamide-N,N'-bis(acryloyl)cystamine) [P(AAm-BAC)] layer. Within the temperature range of 50 °C to 70 °C, the gripper experienced shape transition and performed the gripping motion due to the difference in swelling rate (Figure 10b). Different from conventional thermal-responsive hydrogels such as PNIPAm, P(OEGMA-DSDMA) is biodegradable in a low pH environment. Figure 10c shows the biodegradation process of the gripper when immersed in an acidic environment (pH = 3). The gripper gradually opened and dissolved into the solution after being immersed for four hours. Such a biodegradable gripper has potential biomedical applications in acidic environments such as the stomach.

4.2. Drug delivery

Hydrogels are known to be suitable for biomedical applications because of their extraordinary water content, biocompatibility, and softness.^[112] A great number of researchers have demonstrated the use of stimuli-responsive hydrogels for biomedical applications such as cell culture,^[113] drug delivery,^[114-115] bio-sensing,^[116] and scaffolds.^[117-118] Dai et al. proposed the possibility of using a Pluronic F127 diacrylate macromer (F127DA)-based shape memory hydrogel for drug delivery actuated by NIR radiation.^[53] F127DA is a thermal-responsive hydrogel, and by adding graphene oxide that can absorb NIR light, the composite becomes

light-responsive. Figure 11a shows the photo-response shape-recovery process of this hydrogel. After irradiation under a NIR laser for 240 s, the folded hydrogel fully recovered to its original shape. A drug release testing was conducted for three samples: the original shape at 37 °C, the original shape after 5 minutes of NIR irradiation, and the temporary shape after 5 minutes NIR irradiation. (Figure 11b). As shown, the original shaped-NIR (black curve) and original shaped (blue curve) had similar drug release rates (Figure 11c). However, the temporary shaped-NIR had a lower cumulative drug release (red curve). Since the temporary shape gradually recovered back to the original shape, the drug release rate for the temporary shaped-NIR approached that of the original shape after 8~12 hours of the experiment. The drug release curve for the first 5 minutes of the experiment agreed with the observation (Figure 11d). The difference in drug release rates was due to the different surfaces caused by the shape change of the structure. The twisted temporary shape had a smaller surface area compared to the original shape. As a result, the release of the drug was decelerated. Larush et al. utilized the DLP process to fabricate drug delivery systems, in which the release of the drugs from the printed objects was triggered by pH and shape-dependent swelling.^[93] In this study, the authors demonstrated the utilization of 3D printing to improve the performance of classic solid dosage forms by controlling drug release as a function of pH and surface area, while controlling geometry parameters. The responsiveness of the printed objects enabled tailoring of the release of drugs in oral delivery systems, while the drug could be released at a specific location in the gastrointestinal tract, due to changes in the pH of the system. In summary, these reports show that 4D printing provides the ability to fabricate structures that enable controlling the localization and release rate of drugs.^[119]

5. Conclusion and perspectives

In summary, 4D printing of hydrogels has spurred increasing interest in recent years. The concept of 4D printing is defined as 3D printing structures that are able to transform their shape, along with their property and functionality, upon being triggered by external stimuli. Frequently used AM printing techniques for hydrogels such as DIW, SLA, and DLP, their characteristics and applications, have been discussed in this review. Various stimuli-responsive hydrogels, their properties, and response mechanisms were reviewed, and their applications as 4D printed objects were summarized. These stimuli-responsive hydrogels, the stimuli, the fabrication technologies, and their potential applications are listed in **Table 2**, as a reference for readily understanding the status of this research area.

Although the 4D printing technique has achieved remarkable progress, challenges and opportunities are still present. First, from the perspective of fabrication techniques, it is worthwhile to delve further into the potential of currently available AM fabrication techniques and explore new techniques. Currently, the most amenable printing methods for hydrogels are mainly extrusion-based methods such as DIW, FDM, and vat polymerization methods such as SLA and DLS. These techniques have the drawbacks of relatively low resolution and slow printing speed, high equipment cost, and limitation of material choices due to the requirements of the printing methods. The material jetting and binder jetting methods could be suitable for fabrication of the polymer-based material. However, to the best of our knowledge, the case for employing material jetting and binder jetting to produce 4D hydrogel devices has received little attention. Since material jetting and binder jetting have the advantages of less restrictive material types and higher production speed, it is worth exploring their potential applications in hydrogel material 4D printing. On the other hand, multi-materials, high-speed and high-resolution printing technologies are always desirable.

Secondly, from the materials perspective, the types of stimuli and signal outputs are limited. The response to stimuli by hydrogels is mainly confined to moisture, heat, and chemical environment. Exploring new types of stimuli to trigger hydrogels is necessary in order to widen

the application of 4D printed hydrogel devices. For example, a number of hydrogels having high electrical conductivity and good mechanical strength have been reported.^[34, 120-121] The conductive and stretchable hydrogel has the potential for application as the matrix of electrical- and mechanical-responsive hydrogel composites. On the other hand, the output signal for current 4D printed hydrogel devices is limited mainly to the mechanical and biological; the output signals of hydrogels in other areas are seldom employed for 4D printing. For example, PNIPAm is a frequently reported thermochromic material.^[122-124] However, the application potential of PNIPAm as a thermochromic material in 4D printing has not been fully investigated. The stimuli-responsive hydrogel with electrical-, photo-, and thermal-signal outputs could represent a future research direction that will largely widen the application of 4D printing hydrogels.

Finally, the application of the 4D printed hydrogel device is confined by its limited response and output signal type. Currently, the output signal for 4D printing hydrogel devices is mainly mechanical, the majority of devices are induced by the mechanical deformation of the 3D printed object. A broadening of input/output signal type will largely widen the application of the hydrogel device. For example, by introducing the photo-responsive function, applications such as photoinduced actuator,^[125-126] all-optical switch,^[127] and photodetector^[128] can be achieved. On the other hand, by outputting an electrical signal, the 4D printed hydrogel device can serve as a temperature sensor,^[129] strain sensor,^[130-131] electrical switch,^[132] and so forth. Moreover, by introducing other functionalities such as self-healing and self-cleaning, more multi-functional hydrogel devices will be produced. It is hoped that this summary will broaden research interest and inspire further innovative ideas for the hydrogel-based 4D printing device to satisfy myriads of functional applications and bring these smart devices out from the laboratory and into our daily lives.

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References

Figure 1. Schematic of the diverse 3D AM technologies, stimuli-responsive hydrogel materials and applications of 4D hydrogel-based devices. Adapted from [51-59].

Figure 2. (a) Extrusion of UV crosslinked PLA-based ink from a micronozzle under suitable applied pressure and fast solvent evaporation after extrusion. (b) SEM image of the printed 4D active shape-changing architectures. (c) Demonstration of the shape-changing behavior of the device: the flowerlike 4D configuration could be deformed to the temporary hexagonal shape and could change to the initial flowerlike configuration again upon exposure to heat stimuli. (d) Demonstration of the remote-actuated 4D shape-changing performance of a nanocomposite cylinder in a 30 kHz alternating magnetic field. Reproduced with permission.^[52] Copyright 2016 American Chemical Society. (e) Schematic of the materials synthesis and 4D printing process for the dual-gel accordion structure. (f) Experimental photographs of the actuation tests of the printed baseline accordion structure. The scale bar is 1 cm. Reproduced with permission.^[63] Copyright 2019 Elsevier. (g) 4D printing of a soft octopus robot of hydrogels (scale bars, 1 mm.) and schematics of the octopus robot moving under the driving of a magnetic field on the “x-y” plane. (h) Octopus robot achieved a forward movement when the magnetic field was programmed to move from left to right. Reproduced with permission.^[6] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 3. (a) Representations of fused deposition modeling (FDM). Reproduced with permission.^[51] Copyright 2019 Elsevier. (b) 2D PLA-based circular rings in the hexagonal lattices transformed into hexagons; (c) the rings in the square lattices transformed into quadrangles when heated to 90 °C. Scale bar is 12 mm. Reproduced with permission.^[64] Copyright 2015 Springer Nature. (d) Initial planar shape of the 4D-printed composite sheet (left) and the final flower-like shape after heating and cooling (right). Reproduced with permission.^[65] Copyright 2016 Springer Nature. (e) Shape recovering process of cubic frame under 87 mW cm^{-2} of light source (upper) and 76 mW cm^{-2} of sunshine (bottom). (f) Photo-triggered shape memory behavior of 4D printed sunflower from closed to opened state behaving as the blooming of flowers. Reproduced with permission.^[66] Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 4. (a) Representations of laser stereolithography (SLA) using the “upside-down” configuration. Reproduced with permission.^[51] Copyright 2019 Elsevier. (b) As-cured flat pattern, desolvated origami shape, and swollen flat shape of a six-petal flower 4D origami structure. Insets in the first column are two grayscale patterns for DLP printing. Reproduced with permission.^[70] Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (c) Workflow illustrating the process of fabricating a multi-material structure based on PμSL. (d) Demonstration of the transition between as printed shape and temporary shape of multi-material grippers. (e) Snapshots of grabbing of an object. Reproduced with permission.^[71] Copyright 2016 Springer Nature.

Figure 5. (a) Schematic of a copolymer actuator composed of an active copolymer film (yellow color) and an inactive layer (black color) and its structural changes (involving hydrogen bonds) in response to moisture sorption and desorption. (b) Optical images showed reversible actuation of the 4D aircraft model in response to RH change from 20% to 80%. Scale bars, 1 cm. Reproduced with permission.^[72] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (c) 4D flower shape reverting to a flat configuration upon hydration and recovering the petal shape while drying (dehydration) (Scale bar is 10 mm). Reproduced with permission.^[73] Copyright 2018 Elsevier. (d) Illustration of self-bending/self-twisting mechanisms of 3D printed strip with programmed secondary grooves. (e) Photographs showing self-bending and recovery process of the printed strips with perpendicular grooves on one side (all the scale bars are 3 mm). (f) Photographs showing self-twisting and its recovery process of the printed 0.2 mm thick strips with 45° inclined grooves of width and depth on one side (all scale bars are 5 mm). Reproduced with permission.^[75] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (g) Schematic diagram of the coaxial flow device. The flow rates of inner gas, middle fluid, and outer fluid are marked as Q_1 , Q_2 and Q_3 respectively. (h)

Butterfly-like structure fabricated using asymmetrical bubble hydrogel microfibers as building blocks. (i) Stereoscopic, inverted microscope and SEM images of fiber with an off-centered straight-line arrangement. (j) Relationship between the curvature and flow rate of gas (Q_1). Error bars, s.d. ($n = 5$). Reproduced with permission.^[76] Copyright 2018 The Royal Society of Chemistry.

Figure 6. (a) Drawing of the chain conformations corresponding to the volume fraction profiles at various temperatures. Reproduced with permission.^[78] Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) 4D printed valve swollen in water at 20 °C (left) and the 4D printed valve swollen in water at 60 °C (right). (c) Flow rate of water through the 4D printed valve as a function of time swollen in water at 60 °C. Reproduced with permission.^[79] Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (d) Photographs showing the hydrogel hinge made of the temperature-sensitive PNIPAAm-based top layer and the pHEMA-based bottom layer in the dry state, and the same hydrogel hinge when fully swollen at 20 °C and 60 °C. (e) Images of the box as printed, at swollen state at room temperature and its thermal response at 60 °C. The scale bar is 1 cm. The dashed lines highlight the edge of the hydrogels. Reproduced with permission.^[80] Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (f) Schema to describe the network formation and transformations of 4D ink consisting of agarose, PAM, and laponite. (g) 4D product printed by 4D ink: softening and hardening cycles of an octopus-like gel. Reproduced with permission.^[85] Copyright 2018 American Chemical Society.

Figure 7. (a) Schematic of the 4D fabrication of self-folding hydrogel-based tubes: printing of AA-MA or HA-MA polymer solutions without/ with living cells onto different substrates (left); crosslinking of the printed films with green light (530 nm) and mild drying (middle); and instant folding into tubes upon immersion of the crosslinked films in water, PBS, or cell culture media (right). (b) AA-MA tube responsiveness; schemes (upper panel) and representative photographs (lower panel) of an AA-MA self-folded tube in water after production via the 4D fabrication process (left), then immersed in a 0.1 m CaCl_2 solution, which led to an additional crosslinking of alginate with Ca^{2+} ions, deswelling, and complete unfolding of the tube (middle), and subsequent immersion in a 0.1 M EDTA solution, where EDTA bonded the Ca^{2+} ions from the alginate, leading to refolding of the film into a tube (right). Reproduced with permission.^[91] Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (c) Diagrammatic sketch of the pH-triggered expansion and contraction of the hydrogel. (d) Measurement of expansion ratio of the hydrogel measured with cubic plate (green) and circular plate (red). (e) Experimental diagram of the particle capture process. The inset at the bottom left is the SEM image of the micro-cage in the contracted state. Optical image on the top right corner is the photograph taken when the focus plane is moved onto the microsphere. SEM image on the lower right corner is the micro-cage with a microsphere trapped. Scale bars: 10 μm . Reproduced with permission.^[92] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 8. (a) Magnetic field-driven actuation of D-SAA device set in front of a magnet bore (left) and velocity of buoyant DFeO-SAA device in water as a function of increasing field strength over a 23 cm distance (right). Reproduced with permission.^[95] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) Photograph of the response of the PD3L4F2 MR_NCH in the air or water to a magnetic bar. Reproduced with permission.^[96] Copyright 2019 Springer Nature. (d) Schematic of the fluorescent color change and 4D complex shape change of the macroscopically anisotropic stimuli-responsive polymer hydrogels (MA-SPH). (f) Thermoresponsive complex shape deformation and fluorescent color display of the actuator at flat views. (Photos were taken after filtering the exciting light through an optical filter which can only let 550–1100 nm light to pass through. Scale bars, 5 mm) Reproduced with permission.^[98] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 9 (a) Schematic of a multi-material tri-layer structure consisting of hydrophobic PU top and bottom skins (pink) with a hydrophilic PU core (white). All materials were 4D printed with a low-cost desktop FDM machine. Following printing and upon hydration, the tri-layer bends out-of-plane at the location of the skin gaps and would return to flat upon drying. (b) Actuation of spiral strips from dehydrated to hydrated: In-plane spiral with increasing actuation angle (from left to right) and side and top views of its dehydrated state (upper and middle image), and the side view of its hydrated state (bottom image). All images are of samples in air. Reproduced with permission.^[54] Copyright 2018 Elsevier. (c) Actuation behaviors of asymmetric PAAm/PAAc hydrogel hand actuators. (d) Bending angles of asymmetric PAAm/PAAc hydrogel in aqueous solutions of urea and different salts as functions of soaking time, all at 5 °C. Hydrogel samples were sized 45 mm $\times$ 5.0 mm $\times$ 1.0 mm and synthesized with 150 s of photopolymerization time. Reproduced with permission.^[106] Copyright 2019 American Chemical Society.

Figure 10. (a) 4D macroscopic gripper at different bending positions: i) before gripping the vial, ii) before gripping the vial, iii) in the gripped state, iv) lifting the vial in water at room temperature, v) lifting the vial in air at room temperature, and vi) releasing the vial in water at 70 °C. Reproduced with permission.^[59] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (b) Sequential optical images of photopatterned untethered P(OEGMA-DSDMA)/P(AAm-BAC) bilayer grippers that open on heating and close on cooling in a 1 $\times$ phosphate-buffered saline (PBS) buffer solution. Scale bar indicates a size of 1.5 mm. (c)

Optical video snapshots of the biodegradation of a functional bilayer P(OEGMA-DSDMA) and P(AAm-BAC) gripper in 500 mM ascorbic acid (vitamin C) and 500 mM hydrogen peroxide at pH = 3. All biodegradation experiments were done at an ambient temperature of 37 °C. Reproduced with permission.^[111] Copyright 2019 American Chemical Society.

Figure 11. (a) Recovery process of F127DA/PLGA/graphene oxide hydrogel from its temporary shape to original shape under NIR. (b) Photographs of drug-loaded original shape hydrogels and temporary shape hydrogels. (c) Cumulative release in 12 h from original shape hydrogels at the first 5-minute NIR irradiation (black) and temporary shape hydrogels at the first 5-minute NIR irradiation (red) and original shape hydrogels at 37 °C (blue). (d) First 10 min cumulative release from original shape hydrogels at 5-minute NIR irradiation (black) and temporary shape hydrogels at 5-minute NIR irradiation (red) and original shape hydrogels at 37 °C (blue). Reproduced with permission.^[53] Copyright 2018 Elsevier.

Table 1 Categories of additive manufacturing processes, examples of techniques, forms of raw materials, and pros and cons.

Process category	Examples of technique	Type of raw materials	Form of raw materials	Pros	Cons	Reference
Material extrusion	Fused deposition modelling (FDM) Direct ink writing (DIW)	Polymer	Solid filament or liquid ink	<ul style="list-style-type: none"> • Facile and versatile to customize • Wide range of materials • Low cost • Fast speed of printing • High resolution and accuracy 	<ul style="list-style-type: none"> • Low resolution. • Slow fabrication speed • Anisotropic nature of the printed parts 	[9-11]
Vat polymerization	Stereolithography (SLA) Digital light processing (DLP)	Polymer	Liquid	<ul style="list-style-type: none"> • Good surface finish • High fabrication speed • Low imaging specific energy • Wide range of materials • No support structures required 	<ul style="list-style-type: none"> • Low product mechanical stability • Require support structure and post-curing step 	[15-16]
Powder bed fusion	Direct metal laser sintering (DMLS) Selective laser sintering (SLS)	Metal	Solid powder	<ul style="list-style-type: none"> • Permit recycling of unused raw material • Tougher and more stable product • High part complexity • Multiple build materials with low waste 	<ul style="list-style-type: none"> • Expensive machines • Rough surface finish 	[20]
Material jetting	Multi-jet printing	Polymer	Melted liquid	<ul style="list-style-type: none"> • Wide range of materials 	<ul style="list-style-type: none"> • Unable to recycle support materials • Post-processing may damage thin and small features 	[21]
Binder jetting	Binder jetting (BJ)	Metal, polymer and ceramic	Solid powder and liquid agent	<ul style="list-style-type: none"> • Support structures included in layer fabrication • High fabrication speed 	<ul style="list-style-type: none"> • Post-processing required • Rough or grainy appearance 	[23]

Sheet lamination	Laminated object manufacturing (LOM) Ultrasonic additive manufacturing (UAM)	Polymer and metal	Solid sheet	<ul style="list-style-type: none"> • High fabrication speed • No support structures required • Low warping and internal stress 	<ul style="list-style-type: none"> • Limited available materials • Low resolution • Noxious fumes caused by thermal cutting 	[25-26]
Directed energy deposition	Electron beam melting (EBM)	Metal	Solid wire or powder	<ul style="list-style-type: none"> • High efficiency for repair and add-on features • Suitable for large components 	<ul style="list-style-type: none"> • Poor dimensional accuracy • Limited choice of materials 	[28-29]

Table 2 Frequently reported stimuli-responsive hydrogel matrices, stimuli responded to, suitable fabrication technique, and application of device.

Name of hydrogel	Stimuli responded to	Fabrication technique	Application	Response time	Ref.
PNIPAm (Active material)	<ul style="list-style-type: none"> • Thermal • Moisture (composite with cellulose) • Chemical (response to pH when composite with sodium acrylate or allyl amine) 	DIW	Actuator Microvalve	5-25 min (for thermal and moisture)	[63, 74, 118]
PAAm (Passive material, serve as hydrogel matrix)	<ul style="list-style-type: none"> • Thermal (composite with PNIPAm) • Magnetic (composite with Fe₃O₄) 	DIW	Soft robot	3-5 min (for thermal)	[6]
PEG-PTMG co-polymer (Active material)	<ul style="list-style-type: none"> • Moisture 	Hot pressing molding	Actuator	~50 s	[72]
Cellulose-hydrogel composite (Active component: pulp fibers; Passive component CMC)	<ul style="list-style-type: none"> • Moisture (composite with cellulose) 	DIW	Actuator	Not applicable	[73]
PEG-HEMA co-polymer (Active material)	<ul style="list-style-type: none"> • Moisture 	DLP	Actuator	30 s (for bending) ~100 s (for recovering)	[75]
Alginate (Active material)	<ul style="list-style-type: none"> • Moisture • Chemical (response to Ca²⁺ ion) • Magnetic (composite with Fe₃O₄) • Light (composite with PDA) 	DIW	Actuator Cell-laden	Several seconds (for chemical response) 180-300 s (for light, depends on light power)	[76, 91, 97]
Agarose (Active material)	<ul style="list-style-type: none"> • Thermal 	DIW	Actuator	~30 s	[85]
AAc (Active material)	<ul style="list-style-type: none"> • Chemical (response to pH) 	Stereolithography	Drug release	Not applicable	[92]
PBI-HPEI (Active material)	<ul style="list-style-type: none"> • Chemical (response to pH) 	Not applicable	Fluorescent light emitter	Not applicable	[98]
P(DMAAm-co-SA) (Active material)	<ul style="list-style-type: none"> • Thermal 	Stereolithography	Gripper	5-20 min (depend on temperature)	[59]
PU (Active material)	<ul style="list-style-type: none"> • Moisture 	FDM	Actuator	~100 min	[54]
F127DA (Active material)	<ul style="list-style-type: none"> • Thermal • Light (composite with GO) 	DIW	Drug release	~300 s (for both thermal and light)	[53]

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various functional materials by manipulation of the structure in the nanoscales to achieve the unusual properties.

The emerging field of 4D printing has attracted interest since first introduced in 2013. Stimuli-responsive hydrogel has become a competitive material for 4D printing due to its good deformability, promising biocompatibility, simple manufacturing, and low cost. This review provides a summary of the current progress in hydrogel-based 4D printed objects and devices based on their fabrication techniques, materials, and applications.

Keyword: 3D printing, 4D printing, hydrogels, stimuli-responsive, additive manufacturing

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4D printed hydrogels: fabrication, materials and applications

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