Advances in digital light processing of hydrogels

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Biomedical Materials

TOPICAL REVIEW

Advances in digital light processing of hydrogels

Xingwu Mo[1,2,3], Liliang Ouyang[1,2,3], Zhuo Xiong[1,2,3,*] and Ting Zhang[1,2,3,*]

[1] Department of Mechanical Engineering, Tsinghua University
[2] Biomanufacturing and Rapid Forming Technology Key Laboratory of Beijing
[3] 'Biomanufacturing and Engineering Living Systems' Overseas Expertise Introduction Center for Discipline Innovation (111 Center)
[*] Authors to whom any correspondence should be addressed.

E-mail: xiongzhuo@tsinghua.edu.cn **and** t-zhang@tsinghua.edu.cn

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Abstract

Hydrogels, three-dimensional (3D) networks of hydrophilic polymers formed in water, are a significant type of soft matter used in fundamental and applied sciences. Hydrogels are of particular interest for biomedical applications, owing to their soft elasticity and good biocompatibility. However, the high water content and soft nature of hydrogels often make it difficult to process them into desirable solid forms. The development of 3D printing (3DP) technologies has provided opportunities for the manufacturing of hydrogels, by adopting a freeform fabrication method. Owing to its high printing speed and resolution, vat photopolymerization 3DP has recently attracted considerable interest for hydrogel fabrication, with digital light processing (DLP) becoming a widespread representative technique. Whilst acknowledging that other types of vat photopolymerization 3DP have also been applied for this purpose, we here only focus on DLP and its derivatives. In this review, we first comprehensively outline the most recent advances in both materials and fabrication, including the adaptation of novel hydrogel systems and advances in processing (e.g. volumetric printing and multimaterial integration). Secondly, we summarize the applications of hydrogel DLP, including regenerative medicine, functional microdevices, and soft robotics. To the best of our knowledge, this is the first time that either of these specific review focuses has been adopted in the literature. More importantly, we discuss the major challenges associated with hydrogel DLP and provide our perspectives on future trends. To summarize, this review aims to aid and inspire other researchers investigatng DLP, photocurable hydrogels, and the research fields related to them.

1. Introduction

Three-dimensional (3D) printing technologies facilitate the customization of individual complex structures; hence, they have been widely used in many fields, including industrial manufacturing, medicine, prototype development, architecture, and cultural relic restoration [1]. Due to the advantages of high precision and high speed (compared with other 3D printing technologies), vat photopolymerization-based 3D printing (VPP) has received extensive attention in recent years. VPP is defined as the computer-controlled process of photopolymerization from a vat of liquid material under controlled light irradiation, to produce a solid object for 3D printing. Photopolymerization-based 3D printing (i.e. lithography or light-projection approaches) has seen considerable progress in the past few years and continues to grow.

VPP can be divided into dot and planar printing methods, depending on the different exposure methods. Dot printing methods, including stereolithography (SLA) and multiphoton polymerization (MPP), cure the resins point by point. SLA uses a laser beam scanned in the *XY* plane to photopolymerize a specific pattern; its accuracy depends on the spot diameter. The resolution of SLA can reach 10 μm [2], and it is widely used to construct complex structures with a high resolution for tissue engineering [3]. SLA has been used to fabricate ear-shaped hybrid scaffolds [4] and extracellular matrices to recreate programmed micromechanical environments *in vitro*

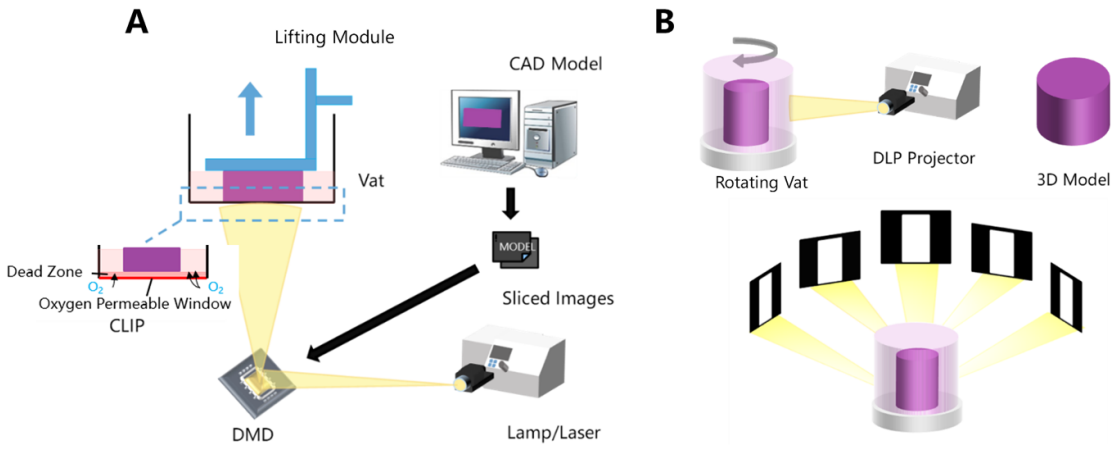

Figure 1. Vat photopolymerization-based 3D printing technologies. (A) Illustration of the printing process of DLP (including CLIP). (B) Illustration of the printing process of volumetric printing.

for 3D cell tissue culture [5]. Similar to one photon absorption in one point (i.e. SLA), MPP applies femtosecond laser pulses that scan and initiate photopolymerization in an small volume, using a two-photon absorption. Printing resolution of MPP can reach ~40 nm [6], so MPP has been used to manufacture low-roughness, high-precision structural devices [7] for applications like tissue engineering and drug delivery [8]. For example, MPP has been applied to print poly(ethylene glycol) (PEG) dimethacrylate devices for controlled drug delivery [8] and to print hybrid biopolymer-based hydrogel 3D grid-like scaffolds to evaluate the cellular viability and biocompatibility of the material [9]. But its further application is limited because only very small (<10 mm) objects can be printed.

Planar printing methods cure a two-dimensional plane simultaneously using both digital light processing (DLP) and its improved versions. DLP employs a digital micromirror device (DMD) to reflect light from a light source, to simultaneously project a 2D image mask into the vat and cure a layer. The lift module moves the printed layer away from its position, and the liquid is quickly replenished to print the next layer; this facilitates the stacking of 3D objects (as shown in figure 1(A)). DLP printing can achieve a printing resolution of 10–100 μm, and the printing speed is greatly improved compared to SLA. Hence, it was widely usedto quickly prepareengineered biological scaffolds, conductive structures, and biosensors [10]. However, the printing speed of this layer-by-layer printing method is limited by layer adhesion and Oxygen inhibition. The printing speed, resolution (usually referring to the *XY* plane) and their respective advantages and disadvantages of SLA,MPP and DLP and its derived technologies are shown in table 1.

To improve the printing speed of DLP, a new method known as continuous liquid interface production (CLIP) was developed [11]. The CLIP method is a more efficient and faster version of DLP; it employs an oxygen-permeable window (a dead zone) [12] (figure 1(A)) at the bottom of the vat for oxygen suppression, to realize continuous rapid printing. The printing speed of CLIP can reach hundreds of millimeters per hour, up to 100 times faster than DLP and SLA [13, 14]. Similar to CLIP, another type of hydrogel-based DLP printer projects lights directly onto a thin layer of fluid-supported precursor; this acts as a floating projection screen to prevent the adhesion problem in DLP printing and realize fast and continuous printing [15]. Another problem with DLP is that the mechanical properties in the layers' stacking direction (*z* direction) are not consistent with the projected plane directions (*x* and *y* directions); we refer to this as the anisotropy problem. To solve this, researchers have proposed a new DLP technology referred to as volumetric printing (VP). VP uses multiple DLP projectors to project masks from multiple angles to the center, and the vat in the center is photopolymerized in rotation to realize the direct one-shot shaping of 3D objects [16, 17] (figure 1(B), detailed in section 2.2). Although referred to as 'volumetric,' it still uses planar DLP projection; hence, it is still regarded as a higher-level version of planar printing. VP can rapidly print cylindrical hollow structures without producing anisotropy in the mechanical properties; thus, it has considerable future potential.

Recently, 3D bioprinting has become one of the fastest growing areas in 3D Printing. Materials represent a key problem in bioprinting; to overcome these issues, researchers have turned to hydrogels. Hydrogels are usually soft and porous, and some hydrogels are highly temperature-sensitive, controllable, and biocompatible. Hydrogels can also be designed by mixing them with other materials to produce a range of good composite properties (e.g. conductivity, magnetic responsiveness, and memory performance) and

Table 1. Main vat photopolymerization-based 3D printing technologies based on hydrogels.

Technique	Advantages	Disadvantages	Printing speed ($mm^3\ h^{-1}$)	Resolution (μm)	References
SLA	• High resolution	• Slow construction for larger objects	$1–10^5$	5–50	[18–21]
MPP	• Higher resolution • Suitable for complex overhanging construct	• High costs • Slow speed • Hard to prepare large-scale objects • Not ideal for cell printing	$10–10^4$	0.5–1	[6, 7, 22–25]
DLP	• High throughput • Suitable for geometrically complex structures	• Hard to produce large-area objects • Hard to prepare high-resolution objects with opaque biomaterials	$10^3–10^5$ $10^4–10^6$ (CLIP)	5–100	[11, 12, 14, 19]

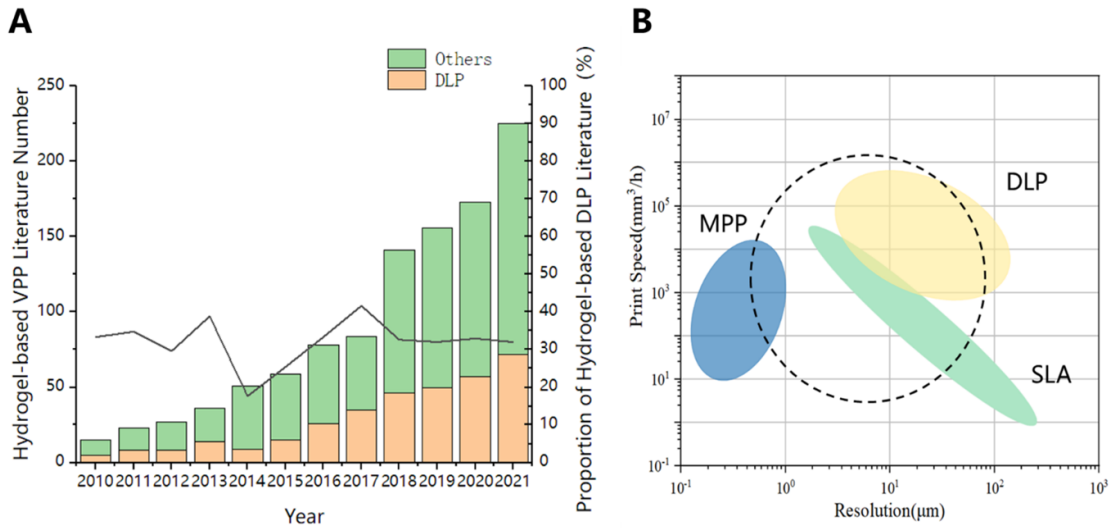

Figure 2. The growth trend of VPP related literature and comparison of resolution and print speed of VPP. (A) The number of literature related to hydrogel-based vat photopolymerization-based 3D printing searched in web of science (http://apps.webofknowledge.com, use 'vat photopolymer* (topic) AND hydrogels(topic)' as keywords). The polyline indicates the proportion of hydrogel-based DLP subject literature in the vat photopolymerization subject literature, as of 1 January 2022. (B) Comparison of resolution and print speed of VPP. The area shown in the circle is the range of resolution and printing speed that we believe is suitable for 3D bioprinting.

support the encapsulation of cells [26]. Owing to their outstanding advantages, hydrogels have become key materials in 3D bioprinting, including bioink-based inkjet or extrusion printing methods. Compared with inkjet or extrusion printing methods, DLP systems do not require fine-grained control of the physical and chemical properties (e.g. viscosity) of the ink and in many cases do not require any supporting materials, especially when printing with hydrogels; this can greatly improve the printing speed and reduce material costs. Thus, photocurable hydrogels have received considerable attention and have gradually become widespread in VPP, especially in DLP 3D printing. However, hydrogels also suffer from problems (e.g. poor printability and poor mechanical properties) attributable to their softness. In recent years, numerous studies have attempted to solve the aforementioned problems through the development of new materials and processes, to broaden the application fields of DLP (especially in biomedical and related fields). DLP has become one of the most popular technologies in the related research, and researchers have combined DLP 3D printing with life science, medicine, microfluidics, flexible materials, and hydrogel-based smart materials to precisely manufacture devices with specific properties. Hydrogel-based DLP printing is becoming a research hotspot in regenerative medicine, flexible devices, and other fields. Since 2010, the number of studies related to Hydrogel-based VPP has increased (especially since 2017), and this field has become a hot topic in 3D printing. More than 200 high-level articles were published in 2021 (figure 2(A)).

Although several interesting reviews have summarized the general progress in DLP 3D printing, few reviews have considered the application of hydrogel-based DLP. Considering the unique properties of hydrogels, we believe it is useful to present a comprehensive review of them. More importantly, current review articles either focus on materials or technologies, while our review highlights a wide range of hydrogel-based applications. The aim of this review is to introduce current studies and the main applications of the hydrogel-based DLP technique, to put forward the main challenges it faces, and to identify its application prospects. In 2020, several high-level papers evaluated hydrogel-based DLP 3D printing in the fields of materials, methods, and medical applications [26, 27]. A comprehensive and profound summary of the DLP technology will have considerable practical value and is necessary and timely. This article will first focus on the problems of hydrogel-based DLP printing, review the latest developments in the hydrogels and printing processes designed to solve these problems (section 2), and focus on the latest applications of hydrogel-based DLP printing in the fields of tissue engineering, regenerative medicine, functional biological microdevices, and soft robots and flexible devices (section 3). Then, we forecast the future prospects and challenges faced by hydrogel-based DLP printing, based on current developments in life science, additive manufacturing, and smart technologies (section 4).

2. Hydrogel-based DLP: advances in materials and fabrication

2.1. Advances in materials used in DLP

A typical VPP system includes three main components: prepolymers, photoinitiators, and light sources [28]. Prepolymers impart the basic physical and chemical properties of the printed parts. Materials commonly used in DLP include hydrogels, resins, ceramics, and other composite materials. The widely adjustale physical and chemical properties of hydrogels have attracted considerable attention in the biomedical field. However, most soft hydrogels have relatively poor mechanical properties; this severely hampers the development in DLP 3D printing. The present section first introduces the hydrogel systems commonly used in DLP printing and introduces the latest advances in hydrogels, including their improved biocompatibilities, stronger mechanical characteristics, and more diverse special properties.

Hence, the latest research into hydrogels has focused on improving their mechanical properties and printability (by ensuring good biocompatibility and degradability) and solving the problem of softness.

Currently, the commonly used hydrogels are primarily divided into two categories (according to the general mechanism and common functional groups employed in polymerization) (figure 3): acrylate hydrogels and thiol-ene hydrogels. In addition, hydrogels based on cationic polymerization have recently attracted the attention of researchers, but there are still few related cationic-based photopolymerizable materials.

Arcylate hydrogels usually have excellent biocompatibility and printability, though they tend to shrink during layer-by-layer printing, causing the printed part to curl and deform [29, 30]. In addition, the material may exhibit non-uniform printability during use, because oxygen in the liquid can react with free radicals, hindering their propagation, sometime even leading to the formation of heterogeneous networks. Acrylate hydrogels have been widely used for the 3D printing of shape memory polymers, highly stretchable soft elastomers, and certain biofunctional materials. These specific applications will be covered in the following sections. However, several acrylate hydrogels exhibit stimuli or cytotoxicity in the uncured state, which limits their application in the biomedical field (especially in tissue engineering). The biodegradation of polymers is another important factor limiting their applications. For good printability and mechanical properties, an increasing number of studies have focused on synthesizing hydrogels with good biocompatibility and biodegradation properties, by introducing acrylate groups into the polymer. For example, the currently synthesized Acrylate hydrogels with good biocompatibility and biodegradability have primarily included polycaprolactone diacrylate (PCLDA) [31], poly(ethylene glycol) diacrylate (PEGDA) [3, 32–34], polycarbonate [35], poly(phthalic acid glyceride) acrylate (PGSA) [35, 36], and diacrylated Pluronic F127(DA-PF127) [37], To further improve cell adhesion, methacrylated natural hydrogel materials [including gelatin methacrylate (GelMA), hyaluronic acid methacrylate and collagen methacrylate] have been introduced in DLP printing. These hydrogels all have good biocompatibility and biodegradability, though they are also all affected by oxygen inhibition. The advantages and disadvantages are shown in table 2.

Thiol-ene hydrogels produce lower shrinkage stress during printing and usually exhibit good biocompatibility. However, some thiol-ene hydrogels suffer from drawbacks such as poor storage stability, strong odor, low stiffnessand poor mechanical properties [38]. Widely used thiol-ene hydrogels include thiol pentaerythritol tetra (3-mercaptopropionate) (PETMP) [10, 39–41]; 1,6-hexanediol diacrylate [39, 42, 43], triallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (TTT); pentaerythritol tetrakis(3-mercaptopropionate) (PE-1); tris (3-mercaptobutyloxyethyl)isocyanurate (NR1) and 1,4-butanediol bis(3-mercaptobutyrate) (BD1) [41]; trimethylolpropane tris(3-mercaptopropionate) [44, 45]; tris[2-(3-mercaptopropionyloxy))isocyan

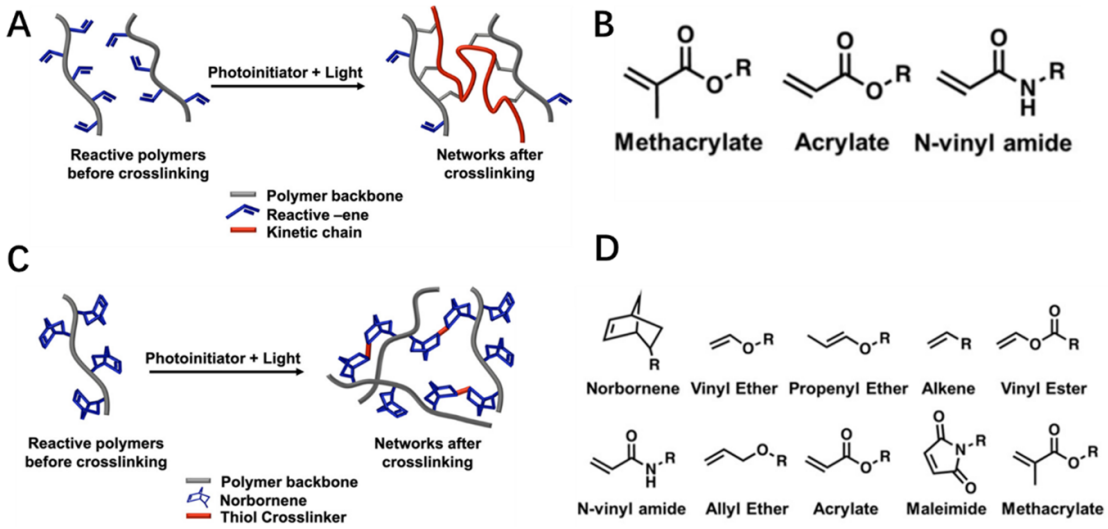

Figure 3. Two types of reaction systems of hydrogels commonly used in DLP. (A), (C) General mechanism for the free-radical chain polymerization and radical-mediated thiol–ene photocross-linking of bioinks and bioresins. (B), (D) Common functional groups employed in free-radical chain polymerization and radical-mediated thiol–ene reactions [26]. Reproduced with permission. Copyright 2020, ACS Publications.

Table 2. Main hydrogels used in DLP 3D printing.

Hydrogels	Advantages	Disadvantages	Reference
PEGDA	• Adjustable mechanical properties	• Low degradation rate • Poor cell adhesion • Oxygen inhibition • Heterogeneous networks	[3, 32–34]
PGSA	• Adjustable mechanical properties • Good elasticity	• High degradation rate and related cytotoxicity • Heterogeneous networks • Oxygen inhibition	[35, 36, 61]
PCLDA	• Good shape memory properties	• Oxygen inhibition • Heterogeneous networks	[31]
DA- PF127	• Reverse thermal-gelation • Ability to gel at low concentrations • Broad range of viscosities	• Poor long-term cell viability	[37]
GelMA	• Good cell adhesion	• Low mechanical strength • Oxygen inhibition • Heterogeneous networks	[49–52]
HAMA	• Good hydrophilicity	• Oxygen inhibition • Heterogeneous networks	[62]
Collagen methacrylate	• Good cell adhesion	• Oxygen inhibition • Heterogeneous networks	[63]
Thiol-ene hydrogels (PETMP,HDDA,TMPMP, TMI,TMPTA3EO)	• No oxygen inhibition • Homogeneous network • Lower shrinkage stress • High toughness	• Poor storage stability • Strong odor • Low stiffness	[10, 39–45, 52]
Cationic hydrogels (DGEBA,CDVE)	• Higher reactivity • Low shrinkage • Good water resistance	• Lack of alternative materials	[47, 48]

urate ethyl ester [41] and ethoxy trimethylolpropane triacrylate [46]. The physical and mechanical properties of thiol-ene networks can be adjusted by varying the functionality and stiffness of secondary thiols. Taking PTEMP, PE-1, NR1, BD1, and TTT as examples, the shrinkage of the secondary thiol-ene systems is 7.6% compared to the acrylate system (Trimethylolpropane triacrylate), with a shrinkage of 13.9%. Objects with a resolution up to 50 μm have been fabricated, exhibiting considerable potential for

the printing of high-resolution 3D optics [41]. Compared with acrylated hydrogels, these materials are less affected by oxygen, resulting in less heterogeneous networks and more consistent mechanical and physical properties.

Another material system that has recently received attention is based on cations rather than free radicals. Such materials undergo photopolymerization via a chain growth process and feature a large number of crosslinking points along the polymer backbone. Cation system-based hydrogels (e.g. diglycidyl ether [47] and 1,4-cyclohexanedimethanol divinyl ether [48]) offer better reaction performances, less shrinkage, and good water resistance; however, the range of alternative materials is currently limited, which may indicate a new research direction for VPP.

Considering the extensive range of biomedical applications, we mainly introduce the latest progress in the research and application of acrylic hydrogels. GelMA hydrogels are representative of this type of acrylate hydrogel and are widely used in tissue engineering scaffolds; they offer good biocompatibility and adjustable porosity, and they are amenable to growth, proliferation, and differentiation [49]. Khademhosseini *et al* demonstrated the suitability of GelMA to support the formation of vascular networks, and they demonstrated that 3D hydrogel constructs contributed to the production of capillary-like networks *in vitro*. They also produced an oxygen-generating hydrogel consisting of calcium peroxide in GelMA scaffolds; this released a large amount of oxygen over a period of five days to alleviate the metabolic stress of the heart side population cells, and it strongly enhanced cell viability [50, 51]. Koffler *et al* reported the use of GelMA and PEGDA to create a 3D bionic hydrogel scaffold suitable for rodent spinal cords. After loading neural progenitor cells, they could promote axon regeneration and repair spinal cord injuries [52].

To further enhance the biocompatibility of hydrogels, decellularized extracellular matrix (dECM) has been extracted, modified, and mixed with other hydrogels when printing biological devices [53]. dECM has good biocompatibility and cell adhesion, so it is often mixed with other hydrogels (such as photopolymerizable hydrogels like PEGDA, GelMA, etc) to prepare bioinks with good biological, physical, mechanical and printablity. However, there are also problems such as batch inhomogeneity in the extraction of dECM. A new personalized airway scaffold was developed using modified *collagen I* extracted from fish scales; it is exhibited non-cytotoxicity and showed good cell viability in a cultured human bronchial epithelial cell line [54]. In another study, after covalent conjugation with fibronectin, the surface of the multilayer scaffold showed efficient cell attachment properties [55]. Natural hydrogels (gelatin, alginate, and hyaluronic acid) have shown tremendous advantages in maintaining and promoting cellular functions. Synthetic hydrogels (e.g. PEG) offer a variety of suitable and controllable properties. To gain better properties, researchers chose to modify natural or synthetic materials(e.g. modify PEG to PEGDA). For example, Park fabricated a bioink from silk fibroinfor DLP in tissue engineering applications. The SF-based bioink (Sil-MA) demonstrates its biocompatibility and printability for different organs with complex structures, including the heart, vessel, brain, trachea, and ear [56].

A suitable cell-loaded biological device for implantation should be structurally integrated and sufficiently similar to human tissues, to adequately support cell adhesion and growth. In recent years, an increasing number of studies have focused upon improving the mechanical properties of hydrogels for tissue engineering. Since adjustalbe mechanical properties can be obtained by adjusting the acrylic acid content, PEG and its derivatives (i.e. PEGDA), PGS and its derivatives (i.e. PGSA), and PCL and its derivatives (i.e. PCLDA) have received extensive attention. For example, mechanical properties can be adjusted using various material formulations (e.g. the concentration of prepolymers). Shaochen *et al* designed and fabricated a 3D PEG scaffold to adjust the elasticity modulus and microstructure; this scaffold can be used to compare the 3D migration characteristics of normal mammary epithelial cells and twisted transformed cells [57].

Studies have also attempted to derive novel hydrogel properties. Once the thermosetting photopolymers form a 3D component via VPP, the hydrogel network can never be reworked, reshaped, repaired, or recycled. A two-step aggregation strategy has benn generated to generate 3D printed processable thermoset plastics; these transform 3D structures into new arbitrary shapes and can repair damaged sites [58]. A novel ink has also been proposed to achieve desirable mechanical properties, by combining a 3D printed composite with a filled silver ink in a hollow channel; this technique has achieved high print speeds, high resolution, good mechanical properties, and low volume shrinkage [59]. Elastic materials with viscoelastic properties have also recently received considerable attention. Researchers have developed a new type of photocurable liquid crystal elastomer; it was optimized for DLP printing and achieved a high dissipation performance up to 27 times greater compared to commercial elastomer [60].

2.2. Advances in the DLP printing process

Although the materials determine the optimal performance of VPP, improvements in the printing process can also improve the printing speed and the hydrogels' mechanical properties. Owing to the limitations of the hydrogels' softnesses, the preparation of devices based on hydrogels with a high Young's modulus remains difficult using DLP. In recent years, to solve the problem of printing resolution and shape

fidelity, considerable research has been devoted to the improvement of DLP printing from the process perspective. For example, Sun *et al* established photocrosslinking theory and a set of standardized methods to quantitatively evaluate printing resolution. In this way, complex biological structures (e.g. ears, hands, and hearts) could be printed accurately [64]. Huh *et al* compared the most commonly used photoinitiator and UV absorber in cell printing, to ensure maximum DLP printability whilst maintaining cell activity [65].

Process-related research to expand the use of DLP represents another hot topic. Li *et al* developed a small, portable DLP printer that supports smartphones, by using an improved design and process; this is expected to offer exciting opportunities for future applications with limited resources, as well as *in-situ* printing [66]. In addition, given the insufficient properties of single material and the uneven *z*-direction mechanical properties of DLP, two further important research fields for the expansion of DLP applications, multimaterial printing and VP, have produced a series of exciting results.

Single materials exhibit limited properties in DLP 3D printing; however, it is difficult to compositely print multiple materials, owing to cross-contamination. The high-resolution, high-speed multimaterial manufacturing of various microstructures with novel functions and optimized properties can be applied in metamaterials, bioinspired soft robots [67], biodevices, optics, and other complicated scenarios. Realizing multimaterial printing and utilizing different materials can also resolve the conflict between the printability and biocompatibility of certain hydrogels.

Over the past ten years, researchers have proposed different methods to achieve multimaterial printing. The first is to switch the materials in the printing device. The basic idea is to change the material in the vat manually/automatically or to switch multiple vats containing different materials automatically during DLP printing. Several researchers have used a rotating platform to implement an automated material-change sequence with vats containing different materials. But the printing process must be stopped when changing vats, which makes the entire printing cycle too time-consuming for cells, particularly when hundreds of layers of material change are required. Wicker and MacDonald developed different strategies to realize multimaterial DLP printing, including the vat exchange, single-bucket and multimaterial exchange, and multitechnology hybrid strategies to implement complex 3D devices, integrated electronic devices, and structures with mechanical, electrical, and biochemical functions [68]. To remove residual hydrogels and ensure printing quality, a newly developed waste exchange mechanism (including air jets to remove uncured hydrogels after each exposure) has also been proposed to assist in multimaterial printing [69].

Microfluidics represents another solution for multimaterial problems. Miri *et al* proposed a multimaterial printing method using a microfluidic device to assist in the single-chamber multimaterial exchange process. A microfluidic device comprising four on/off pneumatic valves was used to switch between different (cell-loaded) hydrogels for layer-by-layer multimaterial printing. Compared to traditional printers, this system offers unique advantages in terms of multimaterial capabilities at a high spatial resolution [70] (figure 4(A)).

Another method is to develop new processes based on the VPP principle. Boydston *et al* proposed a multiwavelength photopolymerization process that utilizes multimaterial actinic space control (MASC) to realize chemically selective control of the material composition. The acrylate component was preferentially cured under long wavelength (visible light) illumination, though epoxide components were cured under short wavelength (UV) illumination; this facilitated the production of multimaterial components containing a hard epoxide network, in contrast to soft hydrogels. MASC formulations spatially control the mechanical anisotropy, chemical inhomogeneities, and spatial scalability of the printed models; this has had a major positive impact on 4D printing [71] (figure 4(B)). Nanomaterial functional inks have also been developed for this purpose: researchers have proposed an internal printing method based on the pores of internal nanoparticles (NPs); this allows the guest material to be locally printed in the host matrix, to realize multimaterial printing [72]. Mao *et al* combined multiple curing-on-demand printheads to produce thin layers composed of different materials during the selective curing of the DLP projector; the remaining uncured materials were effectively cleaned by post-curing equipment, to manufacture 3D multimaterial objects [73].

However, the inherent defect of the DLP 3D printing technology has not been fully resolved. The existing solutions led to longer print cycles, material wastage, and increased costs, which is contrary to the original intention of DLP technology: high precision and rapid one-shot molding. In future, balancing the cost, resolution, and printing speed and implementing the properties of different materials to realize multifunctional multimaterial printing will remain a significantstill challenge.

The layer-by-layer stacking mode of DLP causes anisotropy problems of the biological and mechanical properties between the directions along (*xy* plane) and perpendicular (*z* direction) to the layer. In addition, it establishes geometric constraints (including poor surface quality) and makes it difficult for the DLP to perfectly print hollow structures without support. To solve these problems, a VP method based on DLP projections has been proposed. VP can rapidly print cylindrical hollow structures without anisotropy. A system designed for VP must include three

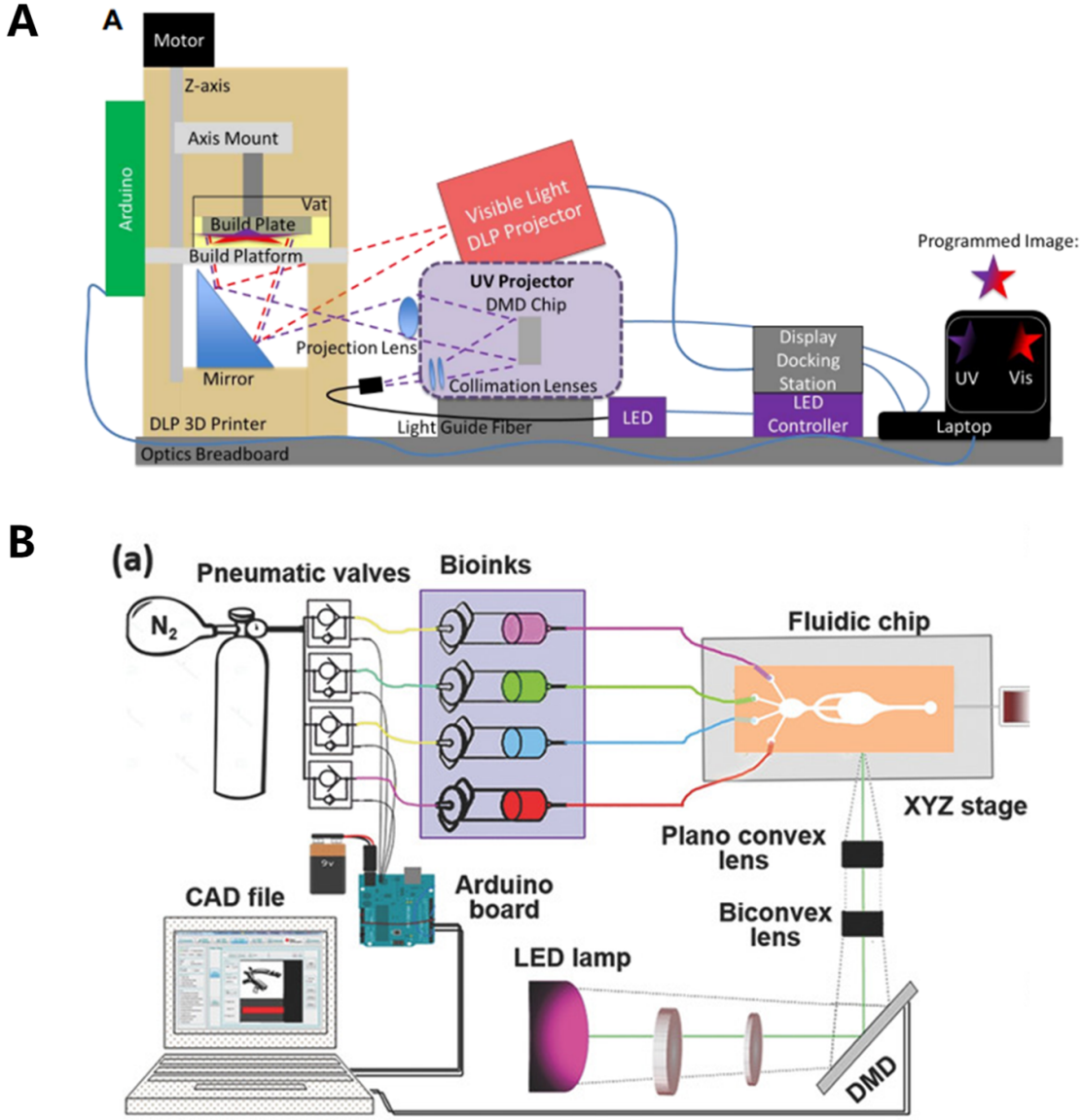

Figure 4. Advances in the printing process of DLP: multimaterial printing. (A) Schematic of the bioprinter, including a UV lamp (385 nm), optical lenses and objectives, a DMD chip, and a microfluidic device [70]. Reproduced with permission. Copyright 2018, Wiley. (B) Schematic of custom multimaterial DLP-AM printer setup. A laptop simultaneously controls both the visible light and UV projector and the printer [71]. Reproduced with permission. Copyright 2019, Springer Nature.

key elements: first, the light field must be patterned at all locations to be cured; second, the lateral intensity distribution of each beam must be adjusted to compensate for resolution and energy absorption in the hydrogels; third, oxygen must be dissolved in the hydrogel, to control the threshold behavior during polymerization.

The earliest VP was reported to produce a hollow structure in a few seconds, using DLP projection. Researchers have used holographic patterning of the light field to fabricate structures. The structure could be constructed under moderate powers (∼10–100 mW) within ∼1–10 s [16] (figure 5(A)). In 2019, Kelly *et al* proposed a manufacturing method that rotated the photopolymer in a dynamically evolved light field; this printed the entire complex object in one complete rotation, avoiding the need for delamination [17] (figure 5(B)). To improve print resolution and print speed, Loterie *et al* [74] used multiple light patterns to illuminate the container from various angles; this produced a 3D distribution of cumulative light doses, allowing the hydrogels to be cured locally as desired. They also developed a high-resolution volumetric method with integrated feedback to ensure precision; with this, complex and hollow parts could be reliably mass-produced at the centimeter level in seconds (<30 s). Regehly *et al* introduced a dual color technique called Xolography, which used photoswitchable photoinitiators to induce localized polymerization under linear excitation from different wavelengths; this facilitated VP of 3D objects with complex structural features and good mechanical functions. Compared with VP without feedback

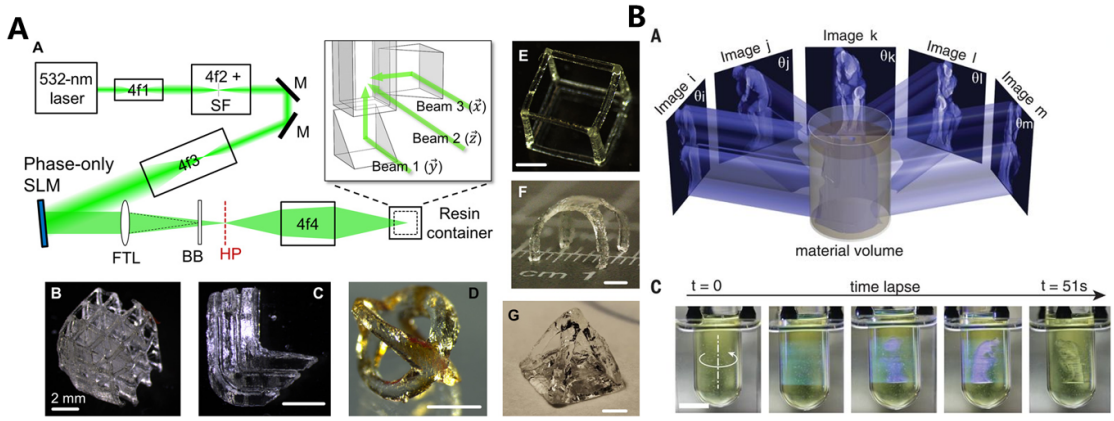

Figure 5. Advances in the printing process of DLP: volumetric printing. (A) Schematic of holographic volumetric 3D fabrication system and example structures. Scale bars, 2 mm [16]. Reproduced with permission. Copyright 2017, AAAS. (B) Schematic of the CAL volumetric fabrication. Scale bars: 10 mm [17]. Reproduced with permission. Copyright 2019, AAAS.

optimization, the resolution of this technique was approximately ten times higher, and the print speed was 4–5 orders of magnitude faster than that of MPP [75].

VP has shown great potential in the field of regenerative medicine, and researchers have also introduced the concept of volumetric bioprinting (VBP) [76], which can fabricate a cell-loaded structure of any size and shape from within a few seconds to several tens of seconds. Recent research has proposed a new thiol-ene hydrogel for VBP. The thiol-ene system with different ratios of isocyanurate and triethylene glycol monomers exhibited a highly adjustable mechanical response and broadened the range of materials and properties available for VBP [77].

However, this method is highly complex and expensive. The printing process places very high demands on the 3D geometry modelling and precise control of the slices, masks, and exposure; this results in a complicated printing process with a complicated corresponding control algorithm. Although the volume-forming method can print some hollow circular structures without support, its characteristic resolution (80–300 μm) does not match that of DLP printing (∼30 μm). Efficient and rapid VP is one of the major challenges in the development of layer-based 3D printing technologies such as DLP.

3. Hydrogel-based DLP: applications

By solving the strength and printability issues and broadening the printing processes of hydrogels, their hydrophilic, soft, and good biocompatibility characteristics can be brought into service, allowing them to be applied in a wider range of fields. This section is divided into three sections. The first section introduces the latest advances in highly biocompatible hydrogels in the fields of 3D cell culture, cell printing, and drug delivery. The second section focuses on the composite physical and chemical properties of hydrogels and reviews their application in the preparation of functional biological microdevices such as microfluidic chips and biosensors. The third section considers the soft and temperature-sensitive properties of hydrogels and summarizes their progress in soft robots, memory polymers, and complex structures used to simulate certain physiological functions.

3.1. Tissue engineering and regenerative medicine

By modifying or combining them with other materials, hydrogels exhibiting certain mechanical properties can be used to prepare biodevices to be implanted *in vivo*, to thereby achieve cell 3D culture and even *in-vitro* cell printing. In addition, *in-vitro* tissue/organ models based on hydrogel materials are widely used for drug screening and treatment applications.

A biological device for implantation (e.g. a scaffold) must be not only biocompatible for cells and human bodies but also nontoxic and degradable; this means it must have minimal impact on the newly formed extracellular matrix (ECM). The implantation device should be porous, strong, and stable, to provide an environment for cell seeding, growth, and differentiation [78]. Hydrogels, which are soft and wet with anisotropic network structures, resemble human tissues and are expected to be widely employed in tissue engineering and biomimetic structures. Several studies have focused on the development of new hydrogel-based biological devices.

The main biological devices employed for implantation are tissue engineering scaffolds. DLP facilitates the fabrication of 3D tissue engineering scaffolds with high-resolution microstructures and controllable biochemical and mechanical properties [79]. The resolution of the tissue engineering scaffold influences its suitability for defect sites, its porosity, its ability to promote nutrient and growth factor delivery, and its cell loading capacity [80]. DLP

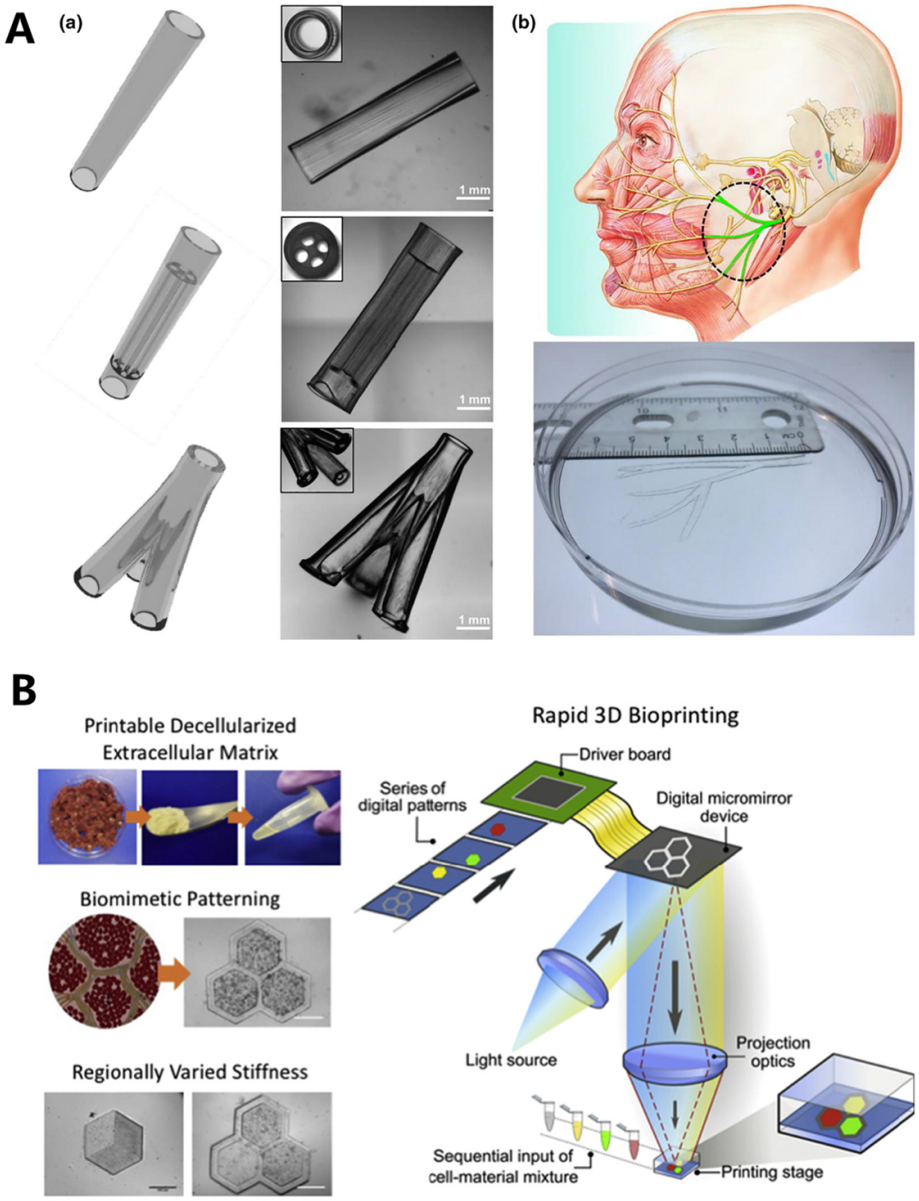

Figure 6. Applications of tissue engineering and regenerative medicine based on DLP 3D printing technology. (A) (a) Various NGC CAD designs (left column) and the corresponding 3D-printed NGCs (right column). (b) 3D-printed human life-size NGC [87]. Reproduced with permission. Copyright 2018, Elsiver. (B) Schematic of the bioprinting process to fabricate dECM tissue constructs based on tissue-specific hiPSCs [92]. Reproduced with permission. Copyright 2018, Elsiver.

3D printing can achieve precise microstructural properties that are critical for producing scaffolds for bones [50, 51, 78, 81] and ears [4], as well as other tissue engineering scaffolds based on hydrogels. The parameters of the system are easy to adjust, which helps to improve the resolution, biocompatibility, and mechanical properties of hydrogel-based scaffolds.

Poly-ε-caprolactone [34], poly(propylene fumarate) [79], PEG, and their derivatives [82] have been widely used in the preparation of biological devices for implantation, owing to their fast printing speed, good photopolymerization properties, and biodegradability. In 2007, a porous, degradable hydrogel scaffold with a well-defined structure comprising 147 μm pores and 730 μm-diameter channels was designed to assist in cell elongation, cell proliferation, and fiber formation *in vitro* [83]. Owing to their perfect overall performance, PEG-based hydrogel scaffolds have been used in the study of human mesenchymal stem cells [84]. However, the cell adhesion of these materials is typically limited; hence, chitosan [85], PCL [86], and other materials are generally used to improve cell affinity.

In addition, hydrogels are often used to create vascularized tissues or biomimetic substitutes for human tissues and organs. For example, a nerve guidance conduit for implantation has been developed to help repair damaged nerves [87] (figure 6(A)).

The use of DLP to prepare porous, degradable tissue engineering scaffolds with complex structures has become a current research trend. However, owing to

material limitations, the mechanical properties and biocompatibility of DLP-prepared tissue engineering scaffolds are still not as good as those of scaffolds prepared by traditional methods. Stronger mechanical properties, personalized shapes, and higher printing accuracies represent the future development directions.

Traditional 2D cell culture models or animal experiments for pharmacological studies are expensive, require a long test period (∼2–3 years), and entail certain ethical risks; furthermore, they cannot realistically simulate the 3D microenvironment of the human body. DLP printing can construct various complex 3D biomimetic microstructures quickly and with high throughput *in vitro* for 3D cell cultures; this is important for studies into drug screening, physiology, and pathology. In recent years, an increasing number of 3D cell culture studies have focused on various normal cells [88] or cancer cells in a specific microenvironment (e.g. liver cancer [89] and breast cancer [82] by using 3D hydrogels. Most of these studies used DLP-constructed hydrogel microstructures to study the behaviors and interactions of cells [especially cells differentiated from induced pluripotent stem cells (iPSCs)] [90] or to assist in the construction of human biomimetic tissues (e.g. natural retinal structures [82]).

The structural and mechanical properties of the tissue significantly influence the process. Compared with the simple protein matrix used in current cell culture systems, the native ECM is rich in a variety of proteins, collagen, glycosaminoglycans, and growth factors; these provide a complex microenvironment to improve cell viability. However, for a long time, the use of an ECM *in-vitro* 3D cell culture has been largely limited to coatings or simple geometries. In recent years, an increasing number of researchers have used ECM- and hydrogel-based DLP to construct microenvironments *in vitro*.

The great challenge in developing an *in vitro* model lies in the limitations of recapitulating the microenvironments of organs, owing to the complex microarchitectures and diverse cell combinations [91]. Based on a rapid DLP, Chen *et al* generated a patterned liver dECM with adjustable mechanical properties for the disease modelling of liver cancer *in vitro* (figure 6(B)) [92]. Alessandri *et al* [93] proposed a microfluidic device that could generate submillimeter-scale hollow hydrogel spheres, to produce a ECM layer coating (with a thickness of a few microns) for 3D cell culture. They encapsulatedcells within the capsules and observed a negligible loss of viability during their further differentiation into neurons. iPSCs can be wrapped in hydrogel- or ECM-based microstructures *in vitro* to proliferate and differentiate into the desired cells. Tissue-matched dECM bioinks provide a favorable environment for maintaining the high viability [94]. In one study, a capsule was decorated with a continuous ECM layer, to mimic the basement membrane of the cell wall; this was used to encapsulate human neural stem cells derived from humaninducednpluripotent stem cell (hiPSC) with negligible loss of activity [93]. spatial patterning of proteins is useful for defining the microenvironments of cultured cells in numerous biological applications. Based on a DLP strategy, any 2D or 3D stable gradient microstructure can be accurately defined from artificial extracellular matrix proteins [95].

Within 3D cell culture, another difficult problem in making/simulating artificial tissues or organs is the creation of blood vessels that transport nutrients to cells inside them. Animal organs contain different fluid networks of physical and chemical entanglement that provide a rich extracellular environment. In addition, organs in the human body also feature independent vascular systems. The ability to fabricate diverse topological microstructures in biocompatible and aqueous environments can alter the research paradigm of biomaterials and tissue engineering. Without sacrificing material or perfusion, Zhu *et al* created prevascularized tissues with complex 3D microarchitectures; these could encapsulate different cells directly in a hydrogel with a precisely controlled distribution, to mimic native vascular tissues [96]. They also generated special shape structures using hydrogels; these are important for the 3D culture of cells *in vitro*. For example, a gear-like microstructure was fabricated by photocrosslinking a PEGDA hydrogel mixed with hepatocytes and fibroblasts in a microfluidic channel, using DLP [97].

Cell printing using cell-containing materials to controllably assemble cells has become a research hotspot. The porous hydrogel structure prepared via DLP can precisely control cell distribution, connection, alignment, and proliferation. In particular, the DLP system provides a noval method for the cells and bioinks that can simulate the key features of the native microenvironment. Therefore, cells can be arranged in a highly ordered geometry and can continuously interact with the surrounding matrix to form tissues with specific functions.

DLP cell printing enables the patterning of various functional elements, including living cells, biomolecules, and NPs. For example, tissue-specific ECM bioinks can be used to create patient-specific tissues, maintaining the high viability and maturation of hiPSC-derived cells via their biocompatibility and almost nonexistent immune rejection. Various hydrogel cell-printing processes and methods for cancer research have also been developed. Using DLP, Zhang *et al* employed an aqueous two-phase emulsion bioink containing two immiscible cells/GelMA mixtures and poly(ethylene oxide) to construct cell-loaded porous hydrogels with three different cell types; this showed enhanced cell viability and proliferation.

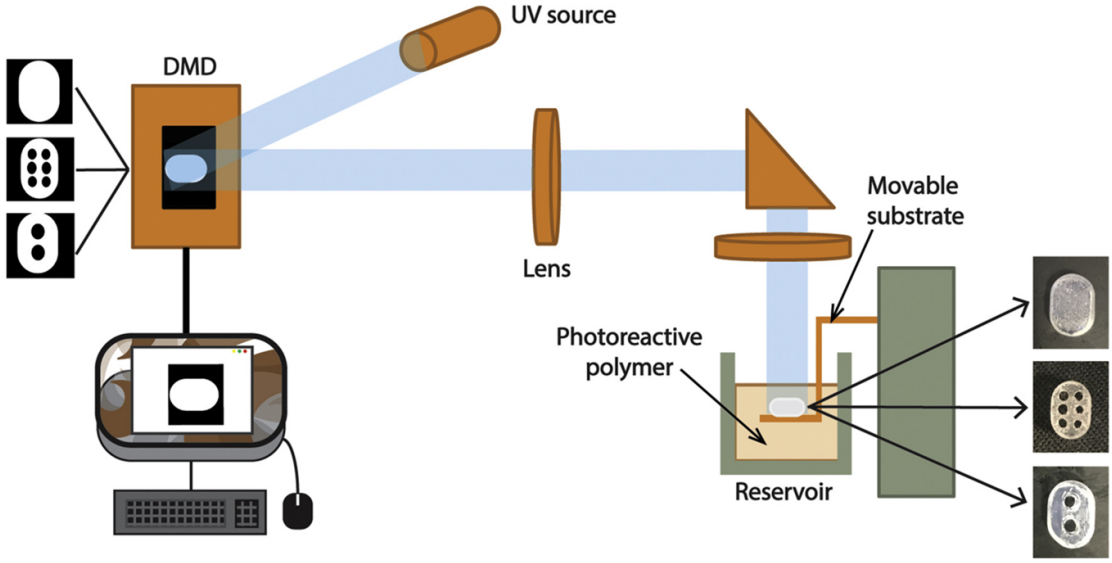

Figure 7. Applications of drug studies based on DLP 3D printing technology. Schematic of the DLP setup to fabricate modified-release tablets [104]. Reproduced with permission. Copyright 2019, Elsiver.

DLP 3D printing has become one of the primary methods for constructing 3D culture models and realizing cell printing. The use of IPS-induced cells and cancer cells for pathology and drug screening research, combined with a more refined and bionic three-dimensional microenvironment construction *in vitro*, shows considerable potential for future research.

Hydrogel-based DLP printing has been applied in drug research and related fields, owing to its customization and high printing accuracy. 3D Printing can be used in different drug development stages, including screening, testing, manufacturing, dispensing, and delivery [98].

Microsphere structures that can encapsulate drugs and deliver them to the location of the disease with timed release have been applied in drug delivery studies. A new type of poly(vinyl alcohol)/hydroxyapatite (HA) composite microsphere with different HA contents for drug applications was developed using DLP [99]. The *in vitro* bioactivity and drug release behavior of the microspheres were evaluated; the results showed microspheres as being good drug delivery vehicles for bone tissue engineering. This method can also be used in high-throughput drug research. Alexander *et al* used DLP to print photocurable inks, to create high-throughput drug delivery systems for the release of antidepressants (paroxetine) [100].

In transdermal systems, drugs do not pass through any metabolic system, resulting in a higher degree of bioavailability; this can be used to promote sustained drug release under control. Vaccination by transdermal drug delivery has become a promising alternative to traditional routes. Different microneedle systems have been fabricated via DLP printing to achieve drug delivery [101]. Microneedle with appropriate geometries can relieve pain and reduce tissue damage during insertion. Another hydrogel-based pyramid and tapered microneedle structure has been applied for transdermal delivery of insulin [102]. DLP 3D printing technology has also been explored as a method to manufacture dosage forms containing drug sensitizers, to reduce the burden of pills and improve patient compliance [103]. Kadry *et al* used DLP 3D printers to prepare PEGDA-based ghost tablets that released the trapped drug but did not disintegrate [104] (figure 7). A simple and effective model based on machine learning was also established to predict the drug release profile of 3D printed PEGDA-based tablets [105].

Smart hydrogels are also available for personalized and programmable medical applications. A drug-loaded system based on 3D-printed pH-responsive hydrogels has been proposed; it showed higher swelling and faster drug release under higher pH, large-surface-area, and complex structural conditions [106].

DLP can create complex geometries for variable drug release kinetics, facile drug therapy personalization, and cost reduction, by manufacturing devices with individualized doses. In addition, DLP facilitates the fabrication of complex micron-sized tissue scaffolds and biomimetic drug test system models for simulated *in vivo* conditions. However, some limiting factors remain (e.g. regulatory issues) and may hinder market development. Research on DLP-based drug delivery requires further investigation [107].

3.2. Functional microdevices

'Functional microdevices' refers to systems and techniques that typically perform tasks on a microscale.

These devices can be used for diagnostic and/or therapeutic purposes in biomedical fields. Functional biological devices range from flexible electronic devices and biosensors to microfluidic chips (some of which facilitate multiple functions). With the improvement in hydrogel-based 3D printing, methods to manufacture functional microdevices with higher complexities and functionalities are also of great significance in the fields of biomedical research, industry, and healthcare. Hydrogel-based DLP 3D printing combines the advantages of softness, scalability, and fast DLP printing speed, to improve the manufacturing speed and scalability of functional biomicro devices and to reduce their cost.

Microfluidic chips have a wide range of applications, including cell cultures, cell sorting, and drug screening. Recent studies have focused on microfluidic chips with high-aspect-ratio microchannels and complex microvalve micropump structures, biosensors, responsive flexible devices, and flexible soft actuators that are responsive to external stimuli (especially the electrical stimuli provided by hydrogels). The use of DLP printing in the manufacture of microfluidic chips can be divided into mold-based and one-step molding methods [108]. The one-step molding method facilitates the construction of microfluidic chips with 3D complex structures and reflects the advantages of DLP printing; hence, we mainly discuss this method. DLP printing eliminates the cumbersome lithography process by using a mask; it acheives higher precision and can prepare structures with smaller feature sizes. Compared with other 3D printing technologies, the minimum channel size of microfluidics manufactured via DLP-SLA is 154 ± 10 μm, and their roughnesses can be as much as 0.35 μm [109].

Currently, microfluidic chip research comprises two approaches. Several studies have focused on preparing high-precision, high-depth-ratio, and high-throughput microfluidic chips; meanwhile, others have committed to preparing functional microstructures such as microvalves and micropumps, using DLP to realize precise control and rapid responses to cells and fluids.

The microchannel is the core structure of the microfluidic chip. The printing of microchannels with high aspect ratios represents an important research topic for 3D-printed microfluidic chips. Gong *et al* developed a mathematical model to help minimize the channel width to four pixels in the construction plane; this laid the foundation for the 3D printing of microfluidics with <100 μm features [110]. Gong *et al* also developed a customized DLP 3D printer with specially designed low-cost custom hydrogels, to realize flow-path cross-sections as small as 18 μm × 20 μm with a flat-panel resolution of 7.6 μm. A novel channel-narrowing technique has also been developed to generate high-aspect-ratio flow channels <25 μm wide and 3 mm tall (figure 8(A)) [111].

Considering its high resolution and ability to print complex structures, DLP printing is suitable for preparing high-density microfluidic devices, such as valves and pumps. A miniature Tesla pump was designed and manufactured with a 43 μm lateral and 30 μm thickness resolution. This could drive a mixer network to generate a microfluidic gradient, which is ideal for flow-sensitive microfluidics [112]. Another microtransporter with a wirelessly controlled Archimedes screw pump mechanism was also designed and demonstrated its potention in realizing space-time-controlled collection, transport, and drug delivery; furthermore, it produced magnetic nanohelices within microfluidic channels [113]. Gong *et al* integrated multiple valves, piping, and valve replacement chambers (DC) on a single microfluidic device and created a compact 3D printing pump. The durability of the 3D printing valves was significantly improved up to one million actuations (figure 8(B)) [114].

In recent years, the 'standardized production' of microfluidics-based organoids has become a research hotspot. Owing to the manufacturing limitations of the core pneumatic membrane valves (PMVs), the microfluidic large-scale integration chips are difficult to apply for tissue cultures and organoids with sizes exceeding tens of micrometers. Compera *et al* developed a process for manufacturing a scaled-up PMV via DLP, and they introduced new developments to highly parallel and high-throughput 3D cell culture and screening applications [115]. Carberry *et al* used DLP to print thioester-functionalized PEG elastomer. The sacrificial thioester elastomer structure can be quickly manufactured in a soft tissue culture medium for 3D characteristic arrays as large as an organoid; this will help when studying the influence of epithelial geometry and spacing on the growth and differentiation of intestinal stem cells [116].

DLP achieves microfluidic printing with higher precision and a greater depth ratio, and it facilitates the printing of microvalves and micropumps with complex structures, thereby enabling the expansion of microfluidic chip functions (e.g. the 'standardized production' of organoids). However, DLP-printed microfluidic chips cannot achieve the same resolution as traditional lithography methods, and the speed of chip preparation is unsatisfactory. These represent important directions for future research into hydrogel-based microfluidic chips.

Conductive materials are important functional materials; they are used as electrodes and wires for signal transmission, heating, and sensing. Electroactive hydrogels, which exhibit large deformations in response to electric fields, have received significant

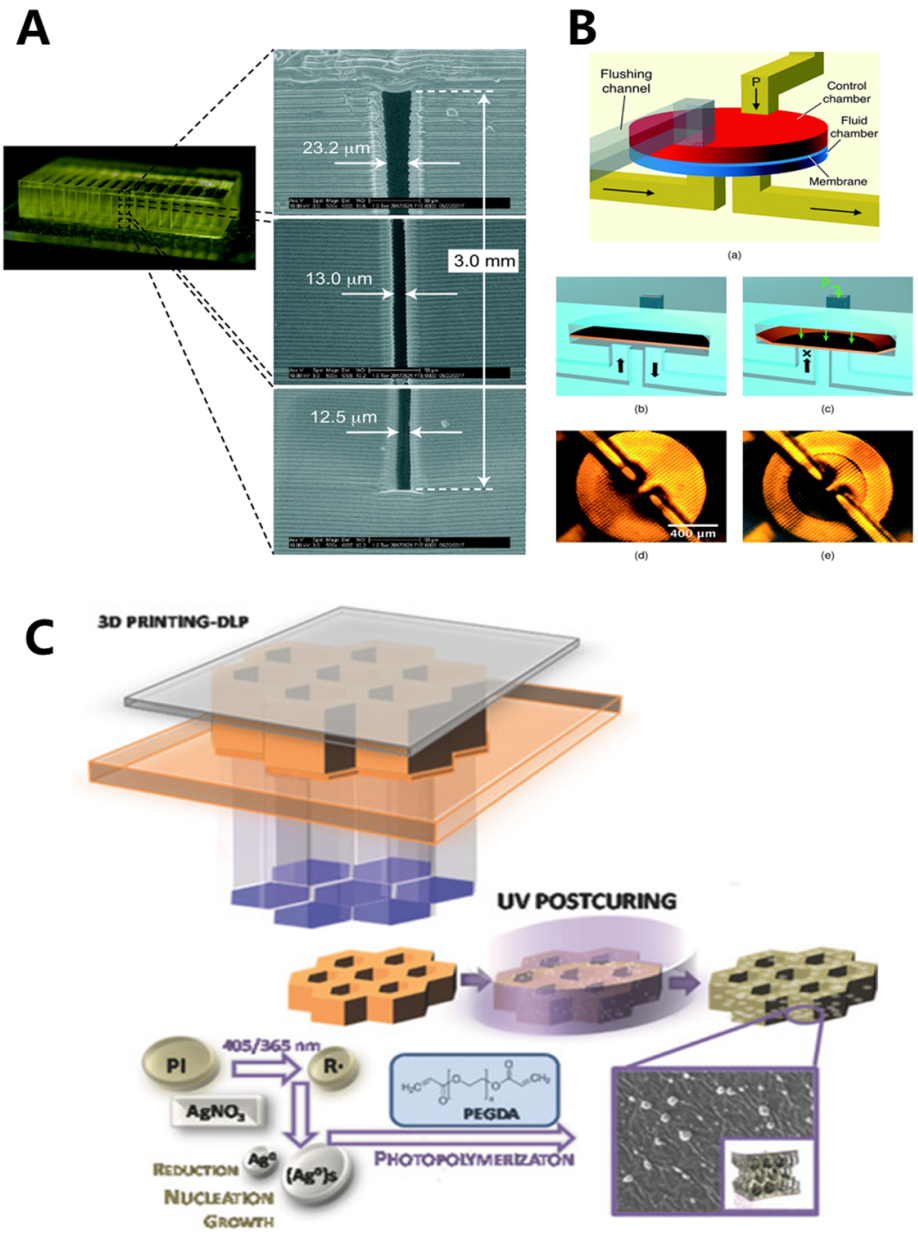

Figure 8. Microfluidic chips and biosensors based on DLP 3D printing technology. (A) 3D printed high aspect ratio flow channel(Physical photograph and SEM images) [111]. Reproduced with permission. Copyright 2017, RSC. (B) CAD designs, schematics and microscope photos of a 3D printed membrane valve and pump [114]. Reproduced with permission. Copyright 2016, RSC. (C) Schematics of DLP setup to form the polyethylene glycol diacrylate structure based on the formation of the silver nanoparticles [121]. Reproduced with permission. Copyright 2016, Wiley.

attention in recent years [107]. Hydrogels can be mixed with materials offering different physical and chemical properties to yield composite properties (e.g. conductivity and magnetic responsiveness). For example, hydrogels can be mixed with carbon and graphene to realize a good electrical conductivity. DLP projectors have been used as an energy source to cure ink mixed with conductive particles such as carbon nanotubes (CNTs) [117, 118], multi-walled CNTs [119], dispersing polyaniline nanofibers and graphene sheets [120] and a variety of conductive NPs (figure 8(C)) [121–125]. A photocurable ink with optimal conductivity and print quality can be obtained by varying the blending ratio of the mixture and printing parameters.

Conventional sensors are often fabricated based on micro-electromechanical systems, which struggle to create complex 3D structures; this makes it difficult to integrate multiple functions. Owing to their good 3D structural forming capabilities, DLP 3D printing has been used to produce integrated sensors. DLP 3D printing has been used to integrate piezoelectric, conductive layers and produce a complete acoustic sensor capable of transmitting electrical signals [126]. Through the use of conductive materials, DLP can assist in the development of smart materials

offering strain sensitivity and shape memory effects; these can be used for biosensors, electrically activated composites, stretchable circuits [119] and flexible electronic devices such as soft robots and artificial muscles [107].

The initial research used a highly ion-conductive hydrophilic polymer (containing cationic or anionic groups) as a highly ion-conductive hydrogel, to fabricate a highly sensitive miniature pH sensor *in situ* [127]. Acrylic hydrogels [e.g. poly(acrylic acid)] are usually used to mix conductive NPs, to produce photocurable inks. Acrylic acid has been used as a functional comonomer to introduce functional groups that can covalently fix immobilize biomolecules upon a microcantilever; this can act as a biosensor in a standard immunoassay protocol [128]. Truby *et al* have created a soft body sensitive actuator governed by a plurality of conductive features, to simultaneously implement tactile, proprioceptive, and thermal sensing [129].

In addition, several researchers have combined metal precursors with hydrogels to produce conductive 3D hybrid multilayer structures. Silver nitrate has been incorporated into photocurable oligomers to produce 3D biosensors [121]. Piezoelectric polymers (barium titanate) were prepared via the incorporation of barium titanate ($BaTiO_3$) to convert the NPs into a photopolymer solution; this solution could be exposed to a mask that could be dynamically changed to generate user-defined microstructures [124].

To prepare 3D structures with different functions, creative processes have also been developed to acquire and assemble conductive particles. In one study, the 3D structure was fabricated by dissolving the metal salt in the starting liquid formulation, where metal NPs were induced *in situ* after heat treatment [122]. Another new particle assembly method used acoustic tweezers during printing to fabricate embedded wires with a 3D structure. Hexagonal acoustic tweezers were used to pattern the conductive lines by aligning and aggregating conductive NPs (e.g. copper and magnetite NPs) and carbon nanofiber-reinforced nanocomposites [123].

With the development of the Internet of Things and flexible devices, soft materials with conductive properties are becoming widespread in the development of wearable devices that require small biosensors to collect data signals. The use of DLP to print soft conductive hydrogels has become an important method in biosensor preparation. However, the applications of biosensors are still limited, and their large-scale application in daily life may still take some time.

3.3. Soft robots and 4D printing

The soft properties of hydrogels offer opportunities in the preparation of soft robots, soft actuators, and so on. In recent years, large, reversible shape-changing soft materials have found potential applications in artificial muscles, soft robots [67, 130], wearable electronic equipment and electronic skin, and dynamic functional architectures. Common hydrogels have limited stretch-ability, and the commercially available 'flexible' hydrogels (with a finite elongation of 90%–100%) are insufficient for advanced applications. In recent years, several high-performance materials, shape memory polymers, and metamaterials have been developed. Together with DLP printing, they can produce flexible devices, especially the high-precision rapid prototyping of soft actuators and grippers.

Soft robotic systems require reasonable degrees of freedom and the ability to undergo large deformations. Owing to the difficulty of fabricating complex molds, these soft robots have limited geometric complexity. DLP printing of elastomers can be used to directly produce highly deformable structures such as soft robot claws, soft balloons, and soft actuators. Commercial photocurable hydrogels with elastic properties can be applied in DLP systems. However, these materials suffer from limitations of poor elongation before breaking and non-adjustable mechanical properties. Due to the lack of suitable materials, the use of DLP printing for stretchable and flexible devices has been limited; however, recent studies have begun to respond to this call.

Patel *et al* investigated high-tensile and high-elasticity photocurable materials. They demonstrated the abilities of certain hydrogels to produce objects capable of withstanding 270% tensile strain, and the printed soft gripper exhibited large local deformations, allowing it to grasp an object [131] (figure 9(A)). They developed a highly stretchable and UV-curable hydrogel method using an acrylamide-PEGDA hydrogel precursor to produce structures offering high resolution (up to 7 μm), fidelity, stretchability (>300%), and biocompatibility [132].

Researchers have demonstrated that the mechanical properties (including stretchability) can be adjusted by adjusting the methacrylate content [133]. Thrasher *et al* developed a series of materials suitable for elastomeric objects, including silicones, hydrogels, and their hybrids. The printed sample exhibited a maximum elongation of 472% [134]. Gomez *et al* proposed a self-healing elastomer system that can achieve an extreme elongation of up to 1000%. These elastomers can be 3D printed as modules, which can be assembled to form a highly complex large-scale functional soft robot [135].

In addition, studies have also focused on adding magnetic materials to photocurable hydrogels, to produce soft actuators and structures that can respond to magnetic fields. Multiple magnetic devices and actuators have been prepared using DLP 3D printing with magnetic and nonmagnetic hydrogels [136]. For example, magnetic Fe_3O_4 NPs have been used to manufacture soft actuators of any shape (via

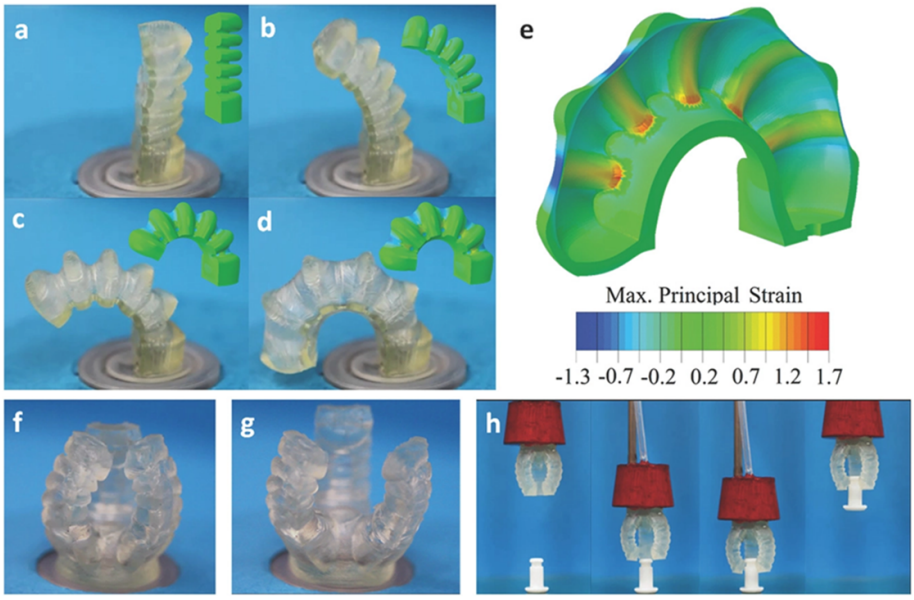

Figure 9. Soft elastomers and soft actuators based on DLP 3D printing technology. 3D printed pneumatically actuated soft actuators with large deformation bending under pressurized air along with FEA simulations and a 3D printed gripper in the process of grabbing an object [131]. Reproduced with permission. Copyright 2016, Wiley.

multimaterial printing) in a freely assembled manner; this can be applied in controllable delivery with remote magnetic control [137].

Magnetic bioreactors are better able to provide a stable force for the cells whilst avoiding direct manipulation of the material. Ajiteru *et al* manufactured a hydrogel embedded in myoblasts, using DLP for magnetic-mechanical stimulation. The magnetic system accelerated the differentiation of mouse myoblasts in the hydrogel, without any evidence of cytotoxicity [138].

Research into soft elastic materials has great application potential in wearable devices and biosensors. However, the applications of these hydrogels usually require special properties that they do not possess on their own, so expanding their hydrophilicity, biocompatibility, and printability in the future will help to further expand their application areas.

4D printing is a concept derived from 3D printing, where a time dimension is added to the process. More precisely, 4D printing uses materials that can be automatically deformed, which is well suited by the softness of hydrogels. 4D printing directly incorporates a designed deformation process into a material, which can be automatically folded into a corresponding shape without connecting any otherequipment. Users can set the model and time, and the materials are deformed into the specific shape within the set time. This self-assembled printing method was first proposed by the Self-Assembly Lab of MIT. They studied the use of rigid polymers and water-strainable materials to produce self-assembled structures. The structure was placed in water and the water-swelling material was bent to drive the hard material to self-assemble [139, 140].

4D printing is achieved by combining 3D printing with the use of soft and deformable materials; it requires 3D printed objects to be able to respond to external stimuli (e.g. water, temperature, pH, and light), and it can change their shape, properties, and functions over time. However, commercially available UV-curable elastomers (whose fracture strain is insufficient for certain applications) require large elastic deformations. Hydrogels are usually soft, have good toughness and deformation properties, respond to stimuli, and can be transformed into a specific shape when simply modified. Hydrogels with these properties have become one of the most suitable materials for 4D printing. These hydrogels are referred to as shape memory hydrogels or smart hydrogels; these have been reported in the printing of high-resolution self-assembled structures [136, 141, 142].

The most-studied hydrogel is the temperature-sensitive shape-memory polymer. Upon heating, the shydrogel softens, relaxing the constraint of the variable elastomer and allowing to transformto a new shape, which can be reprogrammed into other shapes [143]. For example, Cosola *et al* recently prepared a thermosetting H-bond stabilized shape memory polymer that exhibited an excellent, adjustable, thermally triggered shape-memory response [144]. In recent years, more diverse shape memory hydrogels have been developed. Hingorani *et al* [145] proposed adjusting the mechanical properties (e.g. stretching, stiffness, and durability) of commercial

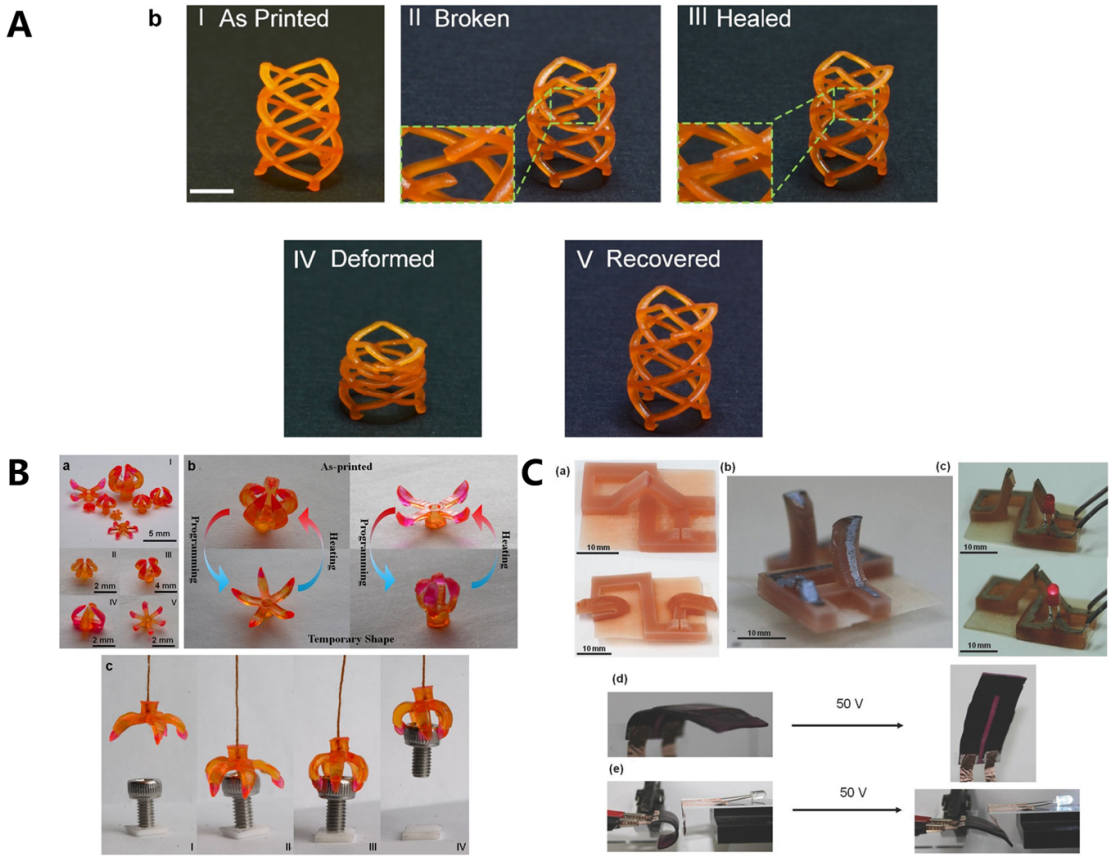

Figure 10. Smart materials based on DLP 3D printing technology. (A) Application demonstrations of SH-SMPs. 3D printed stent (I) as-printed. (II) Broken. (III) Healed. (IV) Deformed. (V) Recovered. (Scale bars: 4 mm) [141]. Reproduced with permission. Copyright 2019, ACS Publishings. (B) Multimaterial grippers with the transition between as printed shape and temporary shape to grab an object [142]. Reproduced with permission. Copyright 2016, Springer Nature. (C) A 3d printed circuit can be turned on and off with the memory shape change of the material [133]. Reproduced with permission. Copyright 2015, Wiley.

UV-cured elastomers by adding materials and cross-linking agents. Shiblee *et al* [146] introduced a novel double-layer poly(N,N-dimethylacrylamide-stearyl acrylate) [P(DMAAm-co-SA)] reversible shape memory hydrogel system, which featured a floral structure that could change its shape after immersed in water; they also developed an 3D soft gripper that could hold, transport, and release substances underwater.

With the development of materials, advances in technologies used for achieving 4D printing have emerged [36, 147]. Ge *et al* proposed a new methodto create high-resolution (up to a few microns) multimaterial structures with thermomechanical properties suitable for achieving controlled shape-memory behavior [142] (figure 10(B)). Most hydrogel-based 4D printed materials are (meth)acrylate thermosets featuring a permanently cross-linked covalent network and cannot be repaired if damaged. Research has reported a dual-network self-healing system and a new printing process for high-resolution and self-healing printing; this has good compatibility and high resolution (30 μm), and damaged parts can self-heal under certain conditions [141] (figure 10(A)).

Smart hydrogels that respond to electrical and magnetic stimuli are important for flexible wearable devices. The layer-by-layer DLP printing of methacrylated semicrystalline molten macromonomers has been reported for the rapid manufacturing of shape-memory circuits. By changing the memory shape of the material, the circuit can be turned on and off [133] (figure 10(C)). This work reveals the potential of 4D printing for the development of flexible electronic devices.

Another new method facilitates the curing of acrylic hydrogel compositions containing biomaterials (especially membrane proteins), to preserve the biological functionality of these proteins; this provides a fourth dimension for the construct. The 4D printing of bioinspired nanomixed electrodes for water-splitting applications [using proton-pumped bacterial rhodopsin, silver NPs (Ag NPs), and CNTs with hydrogels to print photoelectrochemical cells] achieved high durability and low potential onset characteristics [136]. Hu *et al* imitated the dynamic behavior of plant systems to stimuli and achieved the microbionic 4D printing of pH-responsive hydrogels. These could gain multiple degrees of freedom through pH-triggered expansion, contraction, and

twisting, and they mimiced the bionic complex shape deformation [148]. Hydrogels with biometric sites have been used as biosensors. For example, hydrogels can be modified to exhibit biomolecular recognition capabilities, which results in a hydrogel sensing layer with a 3D shape that can self-assemble when it recognizes antibodies [34].

Although a variety of exciting smart hydrogels have been developed, the biocompatibility of these shape-memory polymers and the speed of response deformation are limited; furthermore, the materials typically respond only to a single external stimulus. The application prospects of self-assembled printing components based on shape-responsive hydrogels will promote the development and improvement of shape-memory materials. Future smart hydrogels will develop towards better biocompatibility and more diversified responsiveness.

Natural objects or tissues/organs in the human body typically have complex internal structures, special properties, or complex functions. The fabrication of structures with complex geometries is important for implementing complex functional microdevices. Hydrogel-based DLP 3D printing technology is suitable for constructing complex structures with smaller feature sizes. In recent years, following the rapid development of biomedicine, the simulation of physiological functions has been realized by printing out the complex pipeline networks and microenvironmental microstructures of living organisms. The implementation of complex topology designs has become a research trend. For example, the realization of biomimetic vasculature with a complex structure is an important step in achieving organ printing *in vitro*. Using hydrogels to establish intravascular and multivascular networks, researchers have explored the oxygenation, the flow of human red blood cells during tidal ventilation and near-airway dilation, to simulate the ventilation process of the alveolar and surrounding tracheal networks [149]. In future, the softness of hydrogels will be used to prepare biomimetic structures of complex organs *in vitro*, which will play a positive role in human understanding and exploration.

4. Hydrogel-based DLP: challenges and perspectives

As mentioned above, DLP is still limited by the problems of available materials, multimaterial printing, and anisotropy in the printing process, despite the recent progress. The application of hydrogel-based DLP is still in its infancy and has yet to reach the lives of ordinary people.

Although there have been considerable advances in new photocurable materials, there are still relatively few hydrogels suitable for VPP, especially materials with both good biocompatibility and good mechanical properties. This will represent a major challenge in the future development of DLP printing. Specialized hydrogels with specific rheological, biological (in addition to high biocompatibility), mechanical, physical and chemical properties must be developed over the next few decades.

4D printing eliminates the process of component assembly, achieves superior integration, and is more customizable; therefore, it has broader application prospects and has accordingly received significant research attention in recent years. 4D printing has significant potential in solar energy, medicine, sensors, robotics, and aerospace. A main future trend is that 4D printed products that can be customized by users and changed with external stimulus signals will become a main development direction of the future manufacturing industry. The self-assembly feature will also change the traditional parts-machine assembly mode to a design-fabricate-self-assembly one, which will greatly reduce time and transportation costs and profoundly influence people's lifestyles. For 4D printing, owing to the complex process and harsh requirements of active materials, finding proper materials and accurately controlling the shape deformation are crucial challenges.

DLP 3D printing uses DMD chips for surface exposure. The printing resolution depends mainly on the resolution of the DMD (which is as small as 7 μm) when printing complex structures. However, designing a topology with bionics or other special functions is more challenging than designing a simple and rapid manufacturing process. Considerable research has focused on designing, optimizing, and fabricating complex structures via 3D printing; this will be one of the areas of rapid development for DLP 3D printing.

Artificial intelligence (AI) and big data are powerful tools for solving complex manufacturing problems. In the field of AI (especially machine learning), data play a pivotal role. DLP 3D printing can provide a large quantity of state data at any moment. AI provides a variety of methods with which to improve current 3D printing technologies, including DLP 3D printing from existing data sets [150]. Currently, AI has been applied in 3D printing to facilitate intelligent, efficient, high-quality, mass customizable, and service-oriented production processes [151]. AI algorithms can also be used to optimize material for 3D printing. Recently, a research team from MIT proposed a machine learning method that automatically identified the ideal formulations of DLP printing materials to achieve the optimal mechanical properties after only 30 experimental iterations. This method is expected to be extended to other material design systems, to accelerate the automatic discovery of the ideal materials for 3D printing [152]. Future DLP 3D printing will form an important component of intelligent manufacturing combined with AI.

5. Concluding remarks

Most hydrogels offer the advantages of softness, biocompatibility, and adjustable physical and chemical properties. Combined with the high resolution and high-efficiency characteristics of DLP, hydrogel-based DLP printing has managed to prepare complex structures and devices. The planar printing method not only has opened new avenues in functional microdevices including microfluidics and otherbiomedical devices, but also has showed the potential of the application in tissue engineering, and drug delivery. Despite the current rapid development of the field, several challenges remain that limit its further development. First, more diverse biocompatible hydrogels with specific properties must be developed for 3D (or 4D) bioprinting applications. Second, innovative research is required to solve the multimaterial problems and anisotropy; this should develop new processes to expand the application range of planar 3D printing technology. Currently, 4D printing technology with self-assembly represents a research hotspot, producing 3D materials with biological properties (e.g. biospecific binding sites) that can implement new features in new ways. Special soft and complex structures are of great importance in microelectronics, soft actuators, and biomedical devices; these were difficult to prepare accurately and quickly in the past. With the development of AI and big data technology, the development of DLP 3D printing systems that are sufficiently intelligent and systematic to achieve precise control of the printing process will represent a development direction. We believe that in the future, hydrogel-based DLP printing will flourish as a means of solving existing problems and challenges, and it will help promote the development of biomedicine and humans' self-understanding and quality of life. We believe that this review, which comprehensively lays out (to the best of our knowledge, for the first time) the current state of hydrogel materials, process, and application research, will give researchers and potential practitioners the insights required to help realize these developments.

Data availability statement

No new data were created or analysed in this study.

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Conflict of interest

The authors declare no conflicts of interest.

ORCID iDs

Xingwu Mo https://orcid.org/0000-0003-1201-6459
Liliang Ouyang https://orcid.org/0000-0003-4177-8698
Zhuo Xiong https://orcid.org/0000-0002-9205-086X
Ting Zhang https://orcid.org/0000-0002-3619-2492

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