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Microfluidics-enabled functional 3D printing

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H. Mea[a] and J. Wan[b]

AFFILIATIONS

Department of Chemical Engineering, University of California at Davis, Davis, California 95616, USA

[a]**Also at:** Chemical Engineering, University of California at Davis, Davis, CA 95616, USA.
[b]**Author to whom correspondence should be addressed:** jdwan@ucdavis.edu

ABSTRACT

Microfluidic technology has established itself as a powerful tool to enable highly precise spatiotemporal control over fluid streams for mixing, separations, biochemical reactions, and material synthesis. 3D printing technologies such as extrusion-based printing, inkjet, and stereolithography share similar length scales and fundamentals of fluid handling with microfluidics. The advanced fluidic manipulation capabilities afforded by microfluidics can thus be potentially leveraged to enhance the performance of existing 3D printing technologies or even develop new approaches to additive manufacturing. This review discusses recent developments in integrating microfluidic elements with several well-established 3D printing technologies, highlighting the trend of using microfluidic approaches to achieve functional and multimaterial 3D printing as well as to identify potential future research directions in this emergent area.

I. INTRODUCTION

Additive manufacturing or 3D printing refers to the sequential addition of material into specified shapes made using computer-aided design (CAD) and stands in direct contrast to conventional subtractive manufacturing wherein a substrate material is milled or cut into shape. An assortment of 3D printing methods has emerged that employ different workflows according to material processing applications, mostly relying on layer-by-layer patterning of material, such as thermoplastic filaments,[1,2] metallic powders,[3,4] or solution-based polymeric precursors[5–9] into their final shape. Compared to conventional subtractive manufacturing and machining processes, 3D printing is a more cost-effective and less energy-intensive manufacturing process due to the minimal amount of machining/cutting required and waste material generated (i.e., cutting fluids, lubricants, and material debris).[10] Moreover, in contrast to traditional subtractive or transformative manufacturing (i.e., die-casting and injection molding) that typically relies on economies of scales, 3D printing is highly cost-effective at small scales, making it a widely accessible manufacturing technology for the general public.

A widely coveted goal within 3D printing is the ability to define both form and functional properties across multiple length scales, thus creating printed objects that are both compositionally and functionally heterogeneous. To this end, several 3D printing technologies, such as extrusion-based printing, inkjet, and stereolithography (SLA) have gained pre-eminence among researchers, particularly in the area of biomedical engineering.[6–8,11,12] Widespread adoption of these particular methods can be attributed to steady developments in equipment capabilities (e.g., stepper motors and temperature controls) and the ability to process different materials. Although such 3D printing methods can easily achieve sub-millimeter resolution, with some methods being more amenable to higher print resolutions than others, the ability to handle and mix multiple materials to create heterogeneous prints is still limited, with most commercial 3D printing setups being capable of handling only one ink stream at a time. Ongoing research and development are thus needed to address performance limitations, specifically in terms of the ability to handle multiple materials without sacrificing print resolution or introducing printing defects.

Microfluidic technology, which manipulates fluid flows in miniaturized channels with characteristic lengths between 1 and 100 μm, has developed contemporaneously with 3D printing. The relative dominance of viscous and surface forces in microfluidics results in highly predictable transport behavior, enabling a high degree of spatiotemporal control over fluid composition arising from multiple fluid phases.[13] Consequently, decades of research have yielded a large library of microfluidic device design, each specifically tailored to facilitate a different set of fluidic phenomena according to the desired application (e.g., biochemical analysis,[14,15] separations,[16–18] and material synthesis[19–21]). Given the overlapping length scales with 3D printing technology, microfluidics is well poised to interface with and complement 3D printing technologies by unlocking independent material handling abilities. For instance, continuous microfluidics offers well-controlled mixing and separation capabilities that can be utilized in 3D printing to homogenize or texturize inks prior to dispensing, enabling programmable ink composition and structure. Similarly, droplet-based microfluidics offers controlled droplet generation and unprecedented multiphase flow capabilities that can augment existing 3D printing methods or even inspire entirely new modes of 3D printing.

In this review, we summarize recent developments in microfluidics-enabled 3D printing, emphasizing the benefits presented by microfluidic technology for 3D printing applications. First, the instrumentation and working principles of additive manufacturing methods will be presented. For the biomicrofluidics community, in lieu of the fundamental science related to microfluidics that has been covered extensively elsewhere,[13,22–25] we will specifically provide an overview of the pre-eminent 3D printing methods such as extrusion, inkjet, and stereolithographic (SLA) 3D printing. Following this, we review the recent literature in microfluidics-enabled 3D printing, dividing the discussion into sections roughly corresponding to the 3D printing methods listed above. Reports demonstrating performance enhancement and novel applications of 3D printing specifically enabled by the integration of microfluidic elements and principles are specifically highlighted, along with suggestions for future microfluidics-enabled 3D printing opportunities.

II. WORKING PRINCIPLES AND LIMITATIONS IN CURRENT EXTRUSION PRINTING, INKJET PRINTING, AND STEREOLITHOGRAPHY

3D printing relies on the coordinated deposition/placement of precursor material into CAD-generated 3D shapes followed by post-processing steps to produce the final printed object. While a range of 3D printing methods have been developed, some methods are more favored due to well-characterized working principles, straightforward instrumentation, low-cost, and flexibility in processing different materials. In Sec. II, we will review the working principles of well-established 3D printing methods, including extrusion printing, inkjet printing, and stereolithography, and discuss their limitations that can potentially be addressed using microfluidics.

A. Extrusion printing

Extrusion-based 3D printing relies on the controlled layer-by-layer extrusion/dispensing of material onto a build surface or existing layers of material, culminating in a multilayer 3D printed structure. Materials used in extrusion printing are typically viscoelastic inks that are designed for ease of flow during printing and shape retention post-printing. For many research applications, inks are typically composed of polymer precursors (e.g., epoxies and hydrogels) with other materials, whether it be thinning solvents or solid additives, being added to impart the suitable rheology for extrusion, shape retention, as well as other chemical or functional properties according to the desired application.[26] The final ink is typically extruded through a nozzle as a continuous filament via pressure applied using different controls such as pneumatic controls, pistons, or screw displacement [Fig. 1(a)], while spatial positioning is defined using a series of programmable servo motors. When using constructing multimaterial prints, however, defects are easily introduced when using the common approach of sequentially printing one material at a time, with robust and costly control systems needed in order to minimize such defects. A comparatively simple and streamlined approach to handle multiple inks can be found in microfluidics where researchers have demonstrated the ability to manipulate different fluid streams within a single device. For extrusion-based printing, integrating microfluidic elements into a single printhead provides the user on-the-fly control over incoming fluids to customize composition and architecture of the outgoing ink stream, thereby enabling the construction of

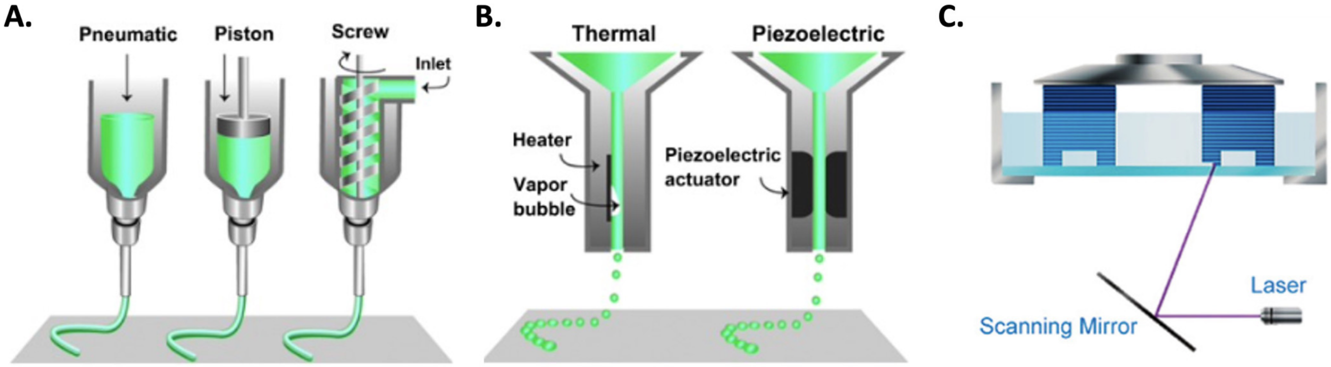

FIG. 1. Three well-established 3D printing technologies. (a) Extrusion-based printing, with three different modes of extrusion being illustrated. (b) Inkjet printing, with two different types of droplet-on-demand techniques being shown.[5] Reproduced with permission from Malda *et al.*, Adv. Mater. **25**, 5011–5028 (2013). Copyright 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (c) Stereolithography (SLA) printing with a scanning laser-based photopolymerization setup.[7] Reproduced with permission from Lee *et al.*, Chem. Rev. **120**, 10950–11027 (2020). Copyright 2020 American Chemical Society.

multimaterial prints with programmable compositional and functional heterogeneity.

B. Inkjet printing

Inkjet technology is similar to extrusion printing, except ink is typically dispensed as uniform discrete droplets at high frequencies. It thus represents one of the earliest examples of microfluidic technology in printing. Traditionally used for 2D patterning, inkjet printing employs either a continuous inkjet or droplet-on-demand approach. The former features a column of liquid that subsequently breaks up into droplets via Rayleigh instability, while the latter features an actuator to generate individual droplets pulse-by-pulse at frequencies as high as 60 kHz [Fig. 1(b)]. Between the ability to generate picoliter-size droplets and the ease of incorporating multiple nozzles within the same inkjet printhead, inkjet printing can easily achieve multimaterial printing and high spatial resolution (10 m). However, along with the strict material property requirements for inkjet printing,[27] the seemingly paradoxical material requirements of breaking up into discrete droplets while retaining its shape post-printing present a significant hurdle in designing inkjet-based 3D printing processes and selecting suitable ink materials. Inks densely loaded with suspended particles typically used in extrusion-based 3D printing are prone to cause clogging in inkjet printheads. Meanwhile, reactive precursor inks that solidify post-printing can be used to achieve layer-by-layer material deposition, but this approach requires a well-controlled sequential deposition of reactants to avoid unwanted reactions. To this end, droplet-based microfluidics may prove especially useful for overcoming or circumventing limitations to inkjet-based 3D printing. Since droplet-based microfluidics has been used extensively to generate and closely manipulate individual droplets for facilitating microparticle synthesis, the design and working principles associated therewith can be readily translated into a 3D printing application, whether via enhancing traditional inkjet printing capabilities or inspiring novel and emergent droplet-based printing approaches.

C. Stereolithography

Stereolithography (SLA) is a light-based additive manufacturing technique that relies primarily on the sequential photopolymerization of resins to form 3D objects. Specifically, standard operation of SLA involves a build stage on which photoresin layers are sequentially applied, typically via immersion into a photoresin vat, followed by photopolymerization of the layer. This process is repeated layer after layer to generate a 3D object. Photopolymerization is typically performed either using a scanning laser for line-by-line patterning [Fig. 1(c)] or digital light processing (DLP) technology in which entire planes/layers are patterned at once. The latter is especially favored for its capacity to dramatically speed up fabrication. At the same time, continuous liquid interface production (CLIP) technology has emerged wherein an oxygen-permeable window is used to create a photopolymerization-inhibitory "dead zone" adjacent to the printing layer that continuously wets the printing layer, thereby enabling controlled and continuous photopolymerization that further speeds up the SLA printing process.[28] As such, vertical print speeds have increased from several mm/h in a traditional layer-by-layer scanning laser method to excess of hundreds of mm/h. A variety of photoresins have been developed for use in various SLA 3D printing applications, including optically clear resins and bioresins for use in cellular/tissue engineering applications.[6–8] The development of a multimaterial SLA 3D printing approach where the composition and functional properties of 3D printed objects are varied across space would require material exchange/switching steps, which, due to the vat-based nature of conventional SLA process, can be prohibitively time-consuming and inefficient in terms of material usage. The targeted introduction and manipulation of fluids offered by microfluidics can thus streamline the handling of different materials (i.e., material switching and intermediate washing steps) and thus facilitate a more material-efficient workflow for multimaterial SLA 3D printing than otherwise achievable.

III. EMERGING MICROFLUIDICS-ENABLED EXTRUSION PRINTING: FILAMENT-BASED MICROFLUIDIC PRINTING

For most applications, nozzle diameters used for extrusion-based printing are on the order of hundreds of micrometers, which is on the high end of the length scale used in microfluidics. This overlap in length scale has led researchers to develop applications incorporating both technologies, including the 3D printing of microfluidic devices or, more relevant to our current discussion, microfluidics-enabled printing. The latter generally refers to using microfluidics technology and principles to augment the capabilities of a 3D printing process, whether it be improving print resolution or enabling multimaterial printing. In Sec. III, the recent literature surrounding the use of microfluidic elements within a single printhead to continuously handle multiple incoming material streams and tune the final composition of the outgoing ink filament is discussed.

A. Core–shell filament produced using coaxial nozzles

Co-flowing fluid streams are a common feature in glass capillary microfluidics where capillaries are aligned coaxially to position fluids and facilitate material synthesis of core–shell microparticles[31,32] and microfibers.[33] Similarly, coaxial nozzles represent a simple and effective method for arranging inks into a core–shell morphology for 3D printing wherein a single filament consists of one material encapsulated within another. The list of possible materials for coaxial extrusion can be extensive, limited only according to the desired application and the ability for material phases to remain distinct from one another. Using a viscoelastic material with higher storage modulus (G') as the encapsulating layer enables an otherwise unprintable ink core to remain in place post-printing. Lorang *et al.* used a hand-machined metallic coaxial needle to encapsulate an unprintable optical precursor ink core (Ormoclear$^{\mathrm{TM}}$) within a fugitive Pluronic F127 sheath. This provided sufficient mechanical support while the core material underwent a 10-min long UV curing process. The net result was a simple process for direct-writing of optical waveguides.[34] Similarly, Frutiger *et al.* used a series of coaxial glass capillaries housed within a larger device to print flexible multilayered conductive wires. In this case, the sheaths of viscoelastic polydimethylsiloxane (PDMS) elastomer provide physical encapsulation, mechanical extensibility, and electrical insulation to the ionically conductive liquid core.[35]

Moreover, aside from providing direct physical support, the outer encapsulating layer can also work synergistically with the core layer to produce new material combinations with unique or superior properties. For instance, Mueller *et al.* designed a coaxial printhead to enable the printing of three-layered epoxy–silicone filaments. The arrangement of a flexible epoxy core followed by a flexible silicone intermediate layer and a brittle epoxy outer layer produced a filament with superior toughness and stiffness, while the recessed-layout of nozzles within a larger housing helps us to minimize the final nozzle diameter as the number of ink streams for encapsulation scales up [Figs. 2(a)–2(c)].[29] Other examples include coaxial filaments of high-density and low-density polyethylene[36] or carbon-fiber epoxy with syntactic foam.[37] The use of coaxial nozzles for generating core–shell filaments can also be found in electrohydrodynamic printing where inks are extruded into filaments using electric fields instead of pressure-driven flow as is typical for extrusion-based printing. Using this method, researchers were able to generate core–shell and hollow microfibers[38–43] whose diameters are smaller than that of the nozzles.

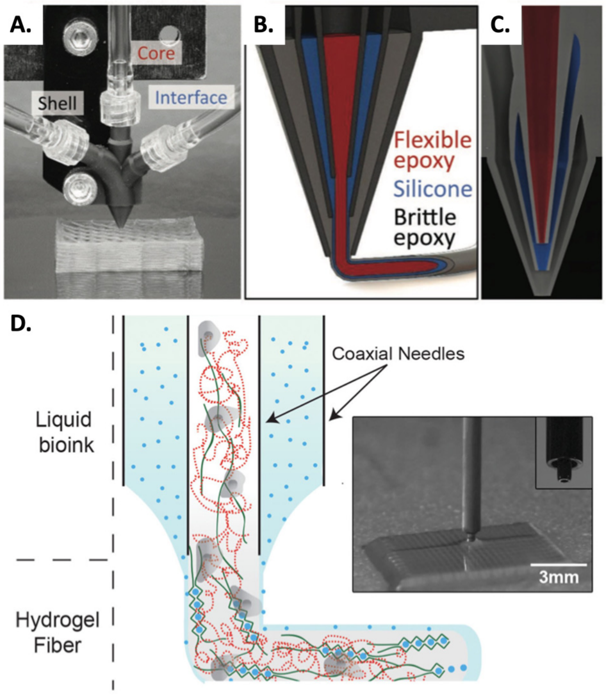

FIG. 2. Extrusion printing of core–shell filaments using coaxial nozzles. (a) Extrusion printing of lattice structures using multicore–shell filaments. (b) Sectional view multicore–shell filaments. (c) Sectional view of the coaxial nozzle.[29] Reproduced with permission from Mueller *et al.*, Adv. Mater. **30**, 1705001 (2018). Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (d) Bioprinting of alginate bioinks using coaxial streams of alginate pre-gel and cross-linker.[30] Reproduced with permission from Colosi *et al.*, Adv. Mater. **28**, 677–684 (2015). Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

In addition to forming a distinct core–shell morphology with clear arrangements of different materials, the coaxial nozzle may be used to facilitate controlled interactions between the different layers of ink. Researchers from the Khademhosseini group developed a microfluidics-enabled process to print gel methacroyl (GelMA)–alginate bioinks. Using a coaxial nozzle, the cell-laden GelMA–alginate blend was encapsulated within a sheath of calcium chloride solution. They hypothesized that an ionic cross-linking reaction of alginate would impart sufficient mechanical integrity for the more bioactive GelMA component to retain its shape while undergoing UV cross-linking. The selection of appropriate printing speeds and ink flow rates through the microfluidic printhead enabled the bioprinting of hydrogel filaments with diameters on the order of hundreds of micrometers, striking a critical balance between uncontrolled ink spread post-deposition due to the low viscosity of the inks and potential nozzle blockage due to the rapid ionic cross-linking reaction of alginate with calcium[30,47] [Fig. 2(d)]. From this base concept or workflow, variations of the same bioprinting process were developed for different applications including that of vascular networks, osteoblasts, muscles, and epithelial cells.[48–50] Overall, the coaxial nozzle is a simple and reliable technique utilizing laminar flow for stratifying different ink materials within the extruded filament, directly paralleling the use of co-flowing fluid streams in microfluidic material synthesis. Glass capillary microfluidics, despite the difficulty in device fabrication, facilitates the encapsulation of one material within another and is thus suitable for direct application in 3D printing of core–shell inks. At the same time, the rise of other nonplanar microfluidic devices made using SLA over the past decade[51] represents a breakthrough in ease of device design and manufacturing that enable researchers to more rapidly develop novel core–shell and multilayered material arrangements for 3D printing applications.

B. Controlling the composition/texture of filaments using swapping and mixing of inks within a single nozzle

One of the key goals of multimaterial printing is the controllable/programmable deposition of different materials/inks at desired locations along the printing path. For extrusion printing, this could be achieved by switching between multiple nozzles mid-print; however, the process calls for advanced or cumbersome control systems in order to minimize the introduction of defects arising from swapping out nozzles or extrusion start-up from the new nozzle. To realize an extrusion-based multimaterial 3D printing process, much research has been focused on designing a single nozzle that can predictably manipulate incoming material streams beyond simply arranging them into a concentric layout as seen in the coaxial nozzle.

Low Reynolds number flow in microfluidics has prompted researchers to explore different mixing schemes in microfluidics to either exploit slow diffusion-dominant mixing or induce turbulence and speed up the mixing process.[52] The integration of similar passive and active mixing schemes within a 3D printhead was investigated as early as 2015. Passive mixing was achieved via the incorporation of fins and grooves along the internal walls of the printhead. For reasonable ink residence times, this method was shown to be incapable of thoroughly mixing ink components, especially when ink viscosity is high.[45] Furthermore, researchers utilized passive mixing as a method of inducing simple and predictable chaotic flows within microchannels to create complex patterns of ink layers, which was subsequently referred to as "chaotic printing."[44,53] This was demonstrated when researchers integrated Kenics static mixer (KSM) elements within a printhead for bioprinting complex micropatterned alginate-based bioink filaments [Figs. 3(a)–3(c)].[54,55] Other more modest instances of mixing printing include creating Janus or biphasic filaments, either by means of a microfluidic Y-channel[30,56] or by bundling microcapillaries together.[57,58] Finally, active mixing via a rapidly spinning impeller within the printhead assembly has been shown to be fully capable of blending and homogenizing incoming inks prior to deposition.[45,46,59,60] This, coupled with programmable control over the incoming flow rates of separate inkstreams, enables real-time control over the composition of deposited inks and opens the possibility of incorporating functional gradients in 3D printed objects [Figs. 3(d)–3(f)]. It is worth noting the utility of computational fluid dynamics (CFD) for modeling-guided experimental design in printhead mixing capabilities[59,61] and even for generating desired micropatterns in 3D printed filaments as in the case of "chaotic printing."[44,53]

Aside from mixing, researchers have also investigated the possibility of fully swapping between ink streams within a single printhead. The buildup of high pressures in extrusion printing, however, presents a challenge for synchronizing flow between different ink lines since mismatches can lead to backflows and lags that result in printing defects. With the understanding of viscoelastic ink flow in microfluidics, researchers can use CFD and

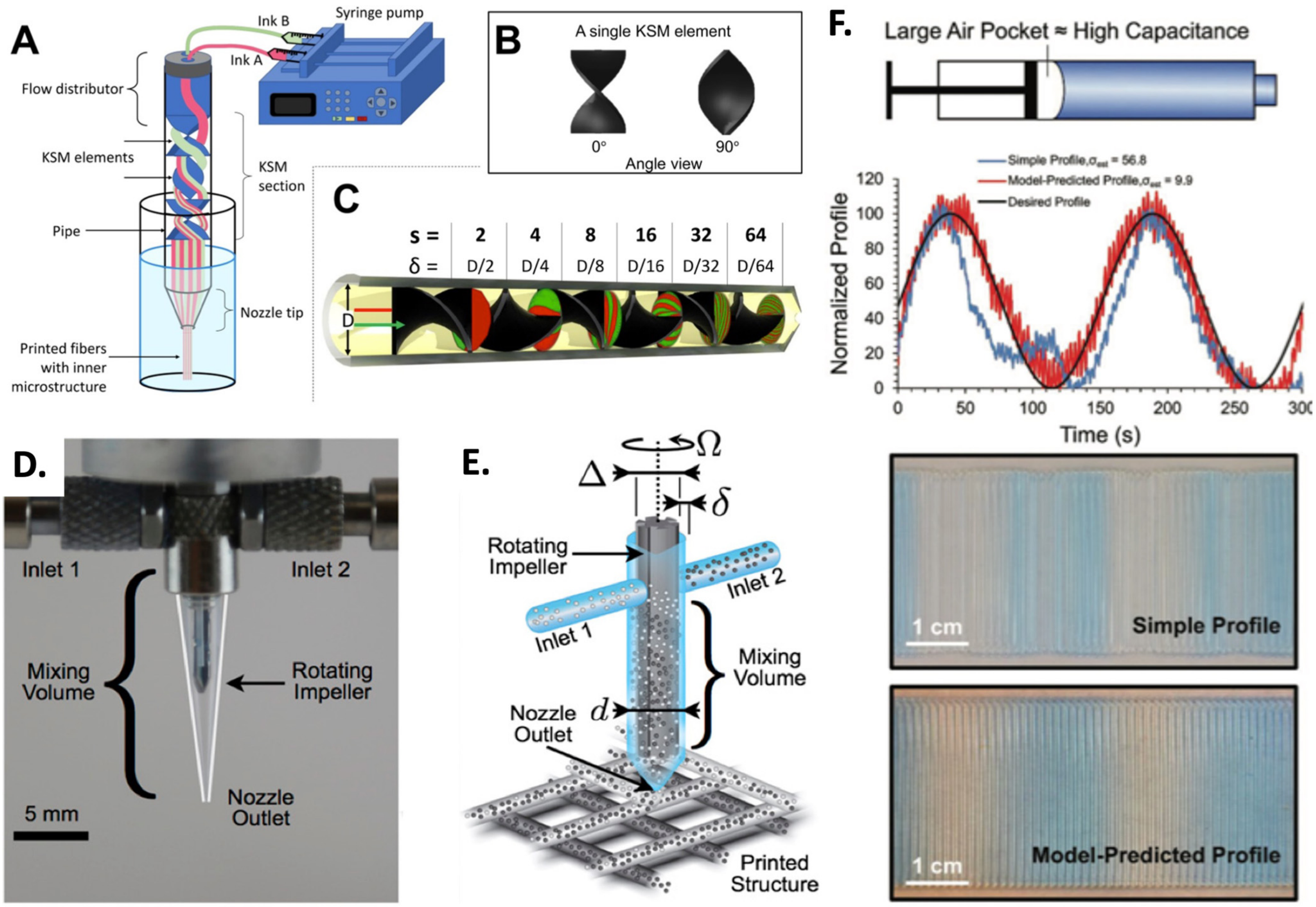

FIG. 3. Extrusion printing with integrated microfluidic mixing strategies. (a) Schematic of fibers printed using continuous chaotic bioprinting. (b) Images of Kenics static mixer (KSM) elements. (c) Modeling fiber microstructure downstream of KSM.[44] Reproduced with permission from Chávez-Madero *et al.*, Biofabrication **21**, 035023 (2020). Copyright 2020 Author(s), licensed under a Creative Commons Attribution 4.0 License. (d) Active mixing printhead using rotating impeller. (e) Illustration of printing using active mixer printhead.[45] Reproduced with permission from Ober *et al.*, Proc. Natl. Acad. Sci. U.S.A. **112**, 12293–12298 (2015). Copyright 2015 National Academy of Science. (f) Microfluidic circuit analogy approach to design precise mixing to match desired profile.[46] Reproduced with permission from Nguyen *et al.*, Adv. Mater. Tech. **4**, 1900784 (2019). Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

other simplified fluidic circuit analogies to predict and achieve robust control over ink flow rates and the rapid switching of ink streams. Hardin *et al.* designed a T-junction printhead capable of seamlessly swapping between two separate streams of PDMS ink. In order to predict the velocity field and flow of the inks, researchers used a microfluidic circuit analogy to model the various components of the printing system such as syringe pumps, viscoelastic PDMS inks, and chambers through which the inks flow. Upon successful modeling, researchers demonstrated predictable and precise control over the ink swapping capabilities of the printhead, thereby enabling on-the-fly control over ink composition while printing.[62] The same research group later used the predictable flow properties of viscoelastic inks in microchannels to design a voxelated printhead consisting of a series of branching and converging ink channels that synchronously swap ink streams to 3D print voxelated matter. The yield-stress properties of inks were shown to be crucial in preventing backflow in the microchannels and enabling stable and predictable swapping of inks in response to pressure-induced flows at frequencies as high as 50 Hz.[63] Another recent study demonstrated the elegant combination swapping and mixing capabilities within a single 3D printhead featuring a Y-junction and expanded conical geometry to accommodate pulsatile pressure-driven flow. Researchers relied heavily on computational modeling to inform the device design (e.g., expanded chamber dimensions) and the range of pressure pulse characteristics (e.g., amplitude, cycle period, duty cycle, and phase shift) required to achieve robust real-time control over ink composition.[64] Overall, progress in understanding and modeling fluid dynamics of viscoelastic inks in microfluidics has enabled researchers to exercise enhanced control over the printed filament properties within an extruded-printing context. Given how the reports listed above have predominantly featured polymers and hydrogels, future work should focus on applying a similar degree of mixing and swapping to a broader variety of ink materials and combinations.

IV. EMERGING MICROFLUIDICS-ENABLED INKJET PRINTING: DROPLET-BASED MICROFLUIDIC PRINTING

Although inkjet printing is primarily associated with 2D patterns, it has nonetheless inspired the idea of using discrete droplets as the building blocks for 3D printed objects. However, commercial droplet-on-demand inkjet has limitations for ink surface and rheological properties in order to facilitate droplet generation, which thereby restricts the range of usable 3D printing inks. With the emergence of droplet-based microfluidics for material synthesis applications (e.g., liposomes, polymersomes, and microparticles), researchers in 3D printing can draw from an additional pool of literature and resources to design new droplet-based 3D printing strategies and applications.

A. Droplet-based 3D printing of metals

Inkjet-based methods for metal additive manufacturing has been a major research focus over the past couple of decades as they represent a desirable simplification from the other metal additive manufacturing techniques that rely on capital-intensive and complex post-processing steps (e.g., sintering, laser annealing, etc.). Outside of low-temperature metals such as lead, Tin, and solder, however, standard inkjet equipment is unsuitable for droplet-on-demand dispensing of metal due to the extreme temperatures involved.[68] To circumvent this, researchers resorted to modify the piezoelectric actuators to ensure the actuators do not heat up past the Curie temperature at which all piezoelectric properties are lost. At the same time, researchers have proposed a number of novel actuation techniques featuring pressure-pulses[69–71] and Lorentz forces[72,73] to induce Rayleigh–Plateau instabilities that lead to droplet breakoff. Besides the physics of droplet breakup, droplet-based microfluidics also offers insights into using electrochemical reactions to synthesize metallic nanoparticles.[74,75] Correspondingly, other droplet-on-demand techniques were developed for metal printing that sidesteps the need for elevated temperatures altogether. In one approach, researchers used electrohydrodynamics to launch metal nanoparticles suspended in volatile solvents in order to print single micrometer diameter 3D metallic structures, similar to electrospraying.[76] Elsewhere, researchers used a redox approach wherein electrodes are oxidized in a reservoir of electrolytes prior to being launched as droplets of solvated metal ions via electrohydrodynamic forces through a glass microcapillary toward a substrate where the ions finally are reduced back into a metal to produce sub-micrometer metallic 3D features [Fig. 4(a)].[65] Further developments in microfluidics-enabled metal droplet-on-demand printing can be geared toward using reduction reactions of metal precursors as a basis for 3D printing metallic structures.

B. Continuous inkjet-based 3D printing

As a means of creating 3D self-standing printed structures, researchers have resorted to using highly reactive precursors that can undergo rapid gelation/polymerization upon deposition and thereby retain sufficient mechanical integrity during printing. In this regard, photopolymers are favored since they can undergo photopolymerization mid-flight prior to contact with the substrate.[77,78] However, when working with two or more highly reactive chemical components, it becomes exceedingly difficult to prevent unwanted or premature ink reactions without robust control systems in place.[79,80] To overcome this, Visser *et al.* first described a setup reminiscent of continuous inkjet where one actuated nozzle was used to launch a droplet train that subsequently collided with a liquid jet launched from another nozzle.[81] With this setup, spherical core–shell alginate particles were formed that could stack on top of one another to bioprint 3D tissue constructs. Following this, other researchers used a similar setup to handle and 3D print other reactive species, including poly(3,4-ethylenedioxythiophene): poly(styrenesulfonate) (PEDOT:PSS)/ionic liquid,[82] polyaniline,[83] and silicones.[84] The design space afforded by this setup is wide, allowing for adjustments to print resolution and even printed ink rheology based on the reaction kinetics and other printing parameters (e.g., droplet ejection frequency, droplet trajectories, and velocity). With appropriate choice of these parameters, researchers reported freeform printing of 3D shapes without the need for supporting materials.[84] Droplets generated from this "in-air" collision approach could be either homogeneous or heterogeneous, the latter being used to 3D print structures with tunable degrees of microporosity.[77,78]

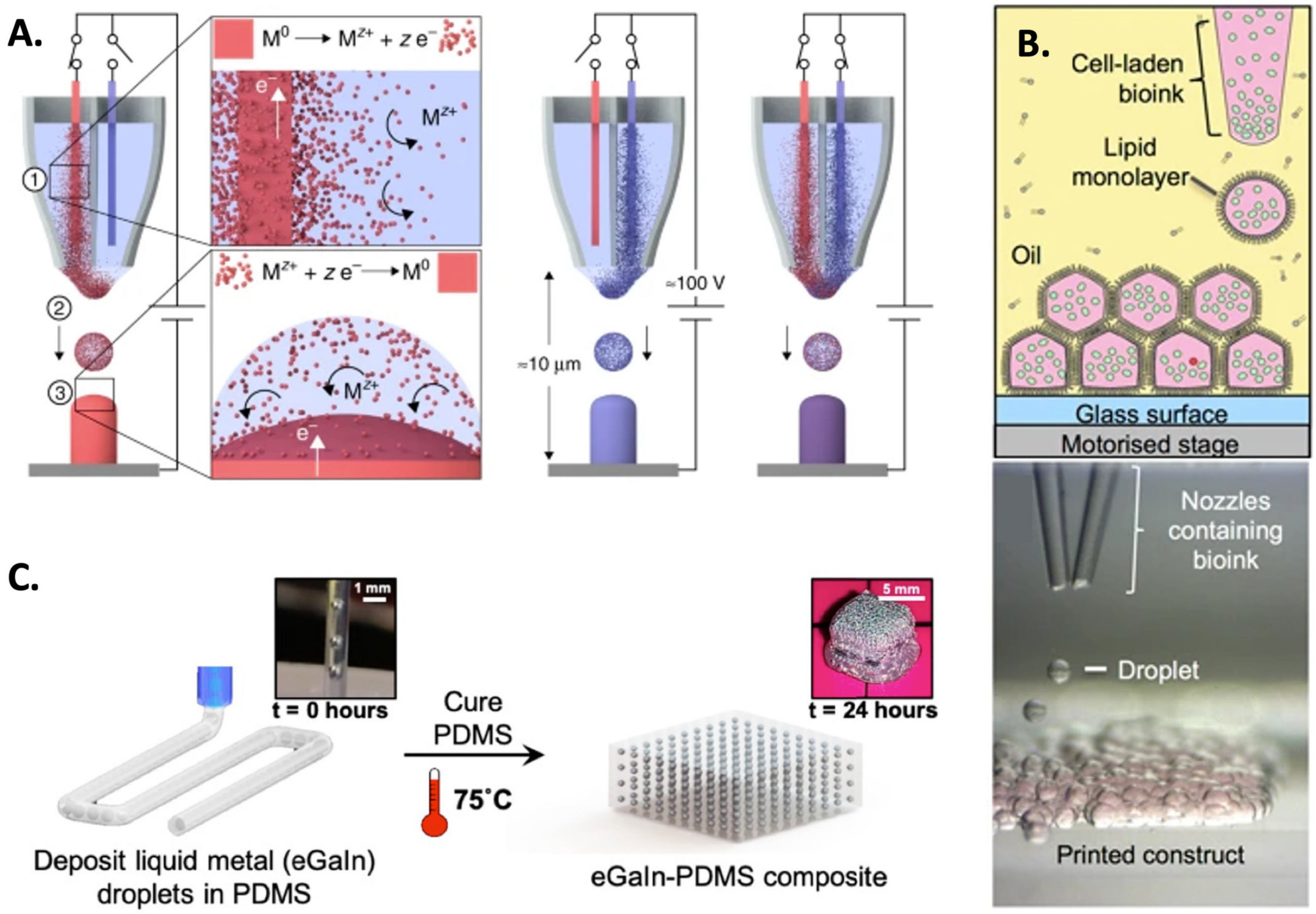

FIG. 4. Droplet-based 3D printing. (a) Electrohydrodynamic droplet generation and subsequent redox of ionic solution for 3D printing metal microstructures.[65] Reproduced with permission from Reiser *et al.*, Nat. Commun. **10**, 1–8 (2019). Copyright 2019 Author(s), licensed under a Creative Commons Attribution 4.0 International License. (b) Droplet network stabilized by droplet interface bilayers (DIBs) and bioprinted into a tissue construct.[66] Reproduced from Graham *et al.*, Sci. Rep. **7**, 1–11 (2017). Copyright 2017 Author(s), licensed under a Creative Commons Attribution 4.0 International License. (c) 3D printing of liquid metal droplets in PDMS filaments.[67] Reproduced with permission from Mea *et al.*, Proc. Natl. Acad. Sci. U.S.A. **117**, 14790–14797 (2020). Copyright 2020 National Academy of Sciences.

C. Multiphase droplet printing

Dispersing droplets into a medium other than air presents the possibility of using interfacial forces to assist in droplet stabilization and assembly. Bayley's group has pioneered the use of a droplet-on-demand technique to 3D print lipid-stabilized droplet networks. Specifically, individual aqueous droplets are dispensed using a piezoelectric actuator and suspended within an oil bath where they are stabilized by lipid molecules at the liquid–liquid interface.[85,86] As each droplet sinks into the bottom of the oil bath, they maintain their roughly spherical shape and adhere to neighboring drops by forming droplet lipid bilayers (DIBs). Researchers subsequently used their droplet-on-demand process of lipid-coated hydrogel droplets in an oil bath for bioprinting high-resolution cellular/tissue constructs, reporting cell viabilities that are higher than those found in extrusion bioprinters while approaching the resolution of inkjet printers (10 m droplet diameters) [Fig. 4(b)].[66,87,88] The presence of DIBs in these droplet networks demonstrated to stabilize the network, thus overcoming the traditional difficulty associated with handling ECM materials that are otherwise unprintable due to the lack of mechanical integrity. Consequently, researchers were able to use this droplet approach to print cartilage, neural, and intestinal tissues[89–91] with prepatterned arrangements of cells. In addition, by incorporating functional particles and proteins into specific droplets within the network, researchers design complex synthetic tissues with internal functional compartments (e.g., ion conductivity) that allow for cross communication within the droplet network, as well as externally responsive compartments (e.g., magnetic sensitivity).[92,93]

In addition to using fluids, researchers have also utilized yield-stress fluid baths to suspend droplets in space as part of a strategy for organizing droplets into 3D geometries, a technique known as embedded printing. Unlike an oil-based medium, yield-stress fluids used in embedded printing allow the deposited ink to remain fixed in place while simultaneously filling up the void spaces left behind by the traveling nozzle used to deposit the ink. While embedded printing is typically used for freeform printing of continuous ink patterns,[94,95] the suspension of individual droplets within a quiescent bath has several benefits. For instance, yield-stress baths are useful for handling and supporting materials that are otherwise unprintable in-air. Using a constant ink flow rate and nozzle travel speed, researchers successfully embedded high surface tension EGaIn droplets with consistent diameters and spacings within a Carbopol bath and organized into distinct 3D structures.[96] Moreover, the quiescent conditions afforded by the yield-stress bath and the precise control of droplet volumes are conducive for facilitating sensitive reactions and processes such as crystallization of active pharmaceutical ingredients in an advection-free environment.[97,98]

Aside from using individual droplets as building blocks, the encapsulating phase itself may be used to form continuous ink filaments containing discrete droplets, similar to the core–shell morphology of filament-based printing except with discretized cores. While the physics associated with droplet generation through multiphase flows, the hallmark of droplet-based microfluidics, has been extensively reviewed elsewhere, its use for 3D printing has remained largely unexplored. Using traditional droplet-based microfluidic devices, researchers reported the simultaneous generation and 3D printing of droplet core–shell inks. As the multiphase inks are deposited layer-by-layer into a 3D structure, the encapsulated droplets are held in place within the continuous phase, much like in embedded printing [Fig. 4(c)]. Through the careful selection of different ink materials and proportions for the droplet and continuous phases, researchers could modify and tailor bulk properties (e.g., mechanical stiffness, optical properties, appearance, thermal responsiveness, and magnetism) as well as intrinsic properties (e.g., cross-linking density, and self-healing).[67,101] Thus, this direct adaptation of droplet microfluidics represents a multimaterial 3D printing strategy that can be adapted for almost any conceivable application. In addition to the impact of ink materials, we had previously noted how selective packing of droplets within the viscoelastic encapsulating phase due to both the droplet generation and printing processes results in highly textured inks with significant mechanical anisotropy depending on the printing path.[67] What remains to be seen, however, is the extent to which droplets within the encapsulating phase (i.e., multiple emulsions) could be reliably manipulated, redistributed, and reorganized using advective forces from multiphase flows, which would enable facile tuning of the bulk functional properties of 3D printed objects.

V. EMERGING MICROFLUIDICS-ENABLED STEREOLITHOGRAPHY: MICROFLUIDICS-BASED INK SWITCHING

With the emergence of SLA for use in biomedical research and other applications, researchers have recently explored the possibility of enhancing SLA-based 3D printing capabilities using

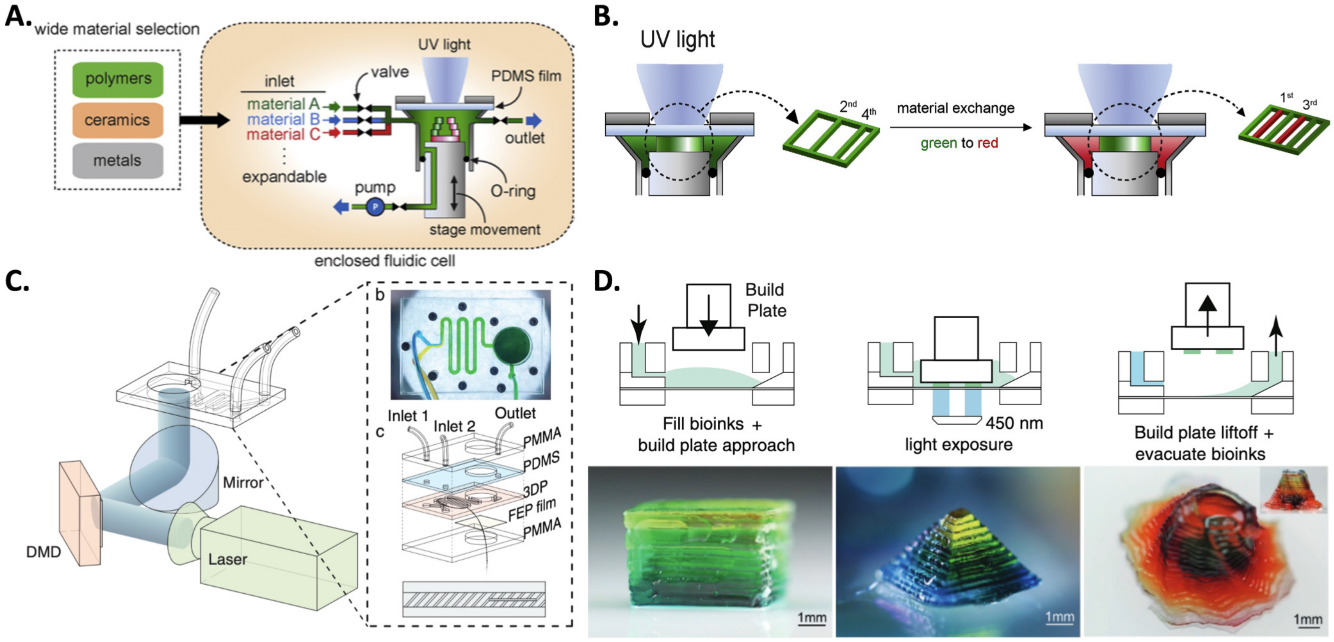

FIG. 5. Multimaterial SLA printing enabled by microfluidic approaches. (a) Microfluidic chamber used to exchange material mid-print to create multimaterial print. (b) Illustration of workflow for generating multimaterial layers.[99] Reproduced with permission from Han *et al.*, Addit. Manuf. **27**, 606–615 (2019). Copyright 2019 Elsevier B.V. (c) Microfluidic device used for chaotic passive ink mixing prior to use in SLA printing. (d) Illustration of workflow for miniaturized build plate setup for 3D printing multimaterial objects.[100] Reproduced with permission from Wang *et al.*, Adv. Mater. **34**, 2107038 (2021). Copyright 2021 Wiley-VCH GmbH.

microfluidics technology. A major challenge associated with SLA is switching inks mid-print as traditional SLA typically uses one photoresin vat throughout the print.[102] An automated robotic fluidic feedstock was first reported in 2018 to dispense and spread various viscous photoresins on the build plate prior to polymerization. Using this setup, researchers printed multimaterial lattice and auxetic structures[103,104] and functional electronic devices.[105] Elsewhere, the use of microfluidic devices has been reported for facilitating sequential material introduction and polymerization. Miri *et al.* reported the use of a standard PDMS microfluidic device for SLA-based 3D printing wherein researchers rapidly switched between different low-viscosity photoresins such as poly(ethylene glycol) diacrylate (PEGDA) and GelMA to create multimaterial bioprinted objects. The reported microfluidic device featured multiple inlets for the various photoresins, branching channels prior to the build area to assist in washing and minimizing material cross-contamination, and a flexible PDMS membrane to enable layer-by-layer photopolymerization in the build area.[106] A similar approach was used by Lamont *et al.* wherein different photoresists were sequentially introduced into a PDMS microchannel and polymerized to create elaborate 3D structures.[107] Other similar efforts reported the use of custom fluidic chambers made from metal or other microfluidic fittings [Figs. 5(a) and 5(b)].[99,108] Aside from ink swapping, microfluidics has also been shown to enable passive mixing of SLA photoresins wherein inks are introduced into a microfluidic mixer to control composition on-the-fly and produce programmable gradients in 3D printed objects [Figs. 5(c) and 5(d)].[100]

In reality, continuous gradients in composition and functional properties in conventional SLA printing are ultimately precluded by its layer-by-layer printing workflow. In contrast, CLIP technology, which uses controlled inhibition of photopolymerization at select regions (often referred to as a "dead zone") via an oxygen-permeable window, enables rapid continuous production of objects from a photoresin.[28] For the purposes of a continuous CLIP-based multimaterial SLA printing setup, microfluidics-based production of hydrogel sheets with composable gradients[109–111] could be a promising method for patterning and continuously feeding photoresin blends to the build plate for photopolymerization. The success for such a setup would be contingent upon the ability of hardware and software to synchronize the sheet patterning, feed rate, build plate vertical travel speed, and optics all while maintaining the presence of the oxygenated "dead zone." As such, this proposed setup would greatly benefit from further developments in sheet patterning and production using microfluidics. Moreover, a simulation work would be indispensable for predicting not only the distribution of photoresin sheet as it travels from the microfluidic device to the build plate but also the oxygen distribution in the photoresin blend that is critical to the CLIP operation.

VI. CONCLUSIONS AND OUTLOOK

Laminar flow within microfluidics enables precise control capabilities over incoming material streams, whether it be organizing material into specific textures/patterns (e.g., core–shell or Janus) or homogenizing or seamless ink swapping. Thus, microfluidics in filament-based printing is conducive for the continuous generation of filaments for 3D printing and exerting on-the-fly control over their microstructure. Similarly, droplet-based microfluidics offers valuable insight into the production and manipulation of individual micro-sized droplets as well as the handling of multiphase flows. Such an insight can be translated into a variety of 3D printing applications to overcome existing limitations, as in the case of inkjet printing, as well as to develop new modes of 3D printing where individual droplets are used as the building blocks. Finally, the precise and controlled manipulation of small volumes of fluids in microfluidics enables streamlined switching and exchanging of photoresin materials, thus facilitating SLA multimaterial 3D printing. There remains many opportunities in this emerging area to explore how microfluidic devices and elements can be directly integrated or adapted for 3D printing applications. Toward this end, we propose the following future directions:

- The high viscosity of inks typically required in extrusion-based printing means that further improvements in print resolutions and speeds will be bottlenecked by the buildup of excessive pressures in printheads. Using electrohydrodynamics instead of pressure-driven extrusion allows the issue of pressure buildup to be sidestepped entirely while maintaining high resolution and speed. Future studies should aim to integrate microfluidics mixing and swapping abilities into an electrohydrodynamic printing setup as well as to understand how ink viscoelasticity affects its ability to be mixed or swapped while being extruded or jetted via electrohydrodynamic forces. Computational modeling would be an invaluable tool to identify critical parameters and to inform the design of experiments for such a multivariable system. At the same time, since electric fields have been widely deployed within microfluidic devices for separations and droplet manipulation applications, the coupling of electrohydrodynamics and microfluidics may yet unlock further capabilities that are relevant for 3D printing functionally heterogeneous objects.
- For integrating microfluidic mixing into 3D printing heads/nozzles, there remains a broad range of passive microfluidic mixing structures in the literature that have yet to report 3D printing ink mixing applications. At the same time, the mixing elements listed in our discussion have characteristic lengths that are on the order of several hundreds of micrometers. Thus there is further opportunity to predict and observe how sub-100 m passive mixing elements such as grooved walls and micro-posts can be used to generate predictable and unique mixing patterns in 3D printing inks. Once again, computational modeling and CFD would be extremely useful for designing and validating the ink mixing capabilities from these passive mixer designs for any ink formulation.
- Droplet-based printing should aim toward adapting more material synthesis reactions inspired by the droplet microfluidics literature to 3D print exotic materials, including, for example, graphene foams for electrode or multiple emulsions for synthetic cells and organelles. In the case of the 3D printing approach using droplets encapsulated within continuous filaments, methods for organizing droplets within 3D printed objects are needed to tune bulk and localized functional properties in printed objects. To this end, computational modeling would be indispensable for parametric study of droplet generation and

distribution within the 3D printable encapsulating phase as well as predicting the resulting spatial variation in functional properties.
- Future work in microfluidics-enabled SLA 3D printing should focus on integrating microfluidics with a CLIP-based approach by developing a reliable workflow to create 3D patterns of multiple materials, thus achieving continuous multimaterial 3D printing. To this end, additional research on continuous microfluidic patterning and production of polymeric sheets would be highly beneficial. Moreover, it would be necessary to perform computational and experimental studies on the distribution of oxygen within a continuously flowing sheet of photoresin as the oxygenated "dead zone" is a critical parameter for CLIP.

Overall, the capacity for precise spatiotemporal control of fluid flows found in microfluidic technology for a variety of applications means that there are numerous opportunities for using microfluidics to enhance existing 3D printing technologies. The availability of computational modeling (e.g., CFD) and experimental tools from the extant literature facilitates the continuous design and validation of microfluidics-enabled 3D printing, which would enable yet greater 3D printing capabilities and even inspire new additive manufacturing technologies for next-generation fabrication capabilities.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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