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Feature

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Evaluation of 3D Printing and Its Potential Impact on Biotechnology and the Chemical Sciences

Nearing 30 years since its introduction, 3D printing technology is set to revolutionize research and teaching laboratories. This feature encompasses the history of 3D printing, reviews various printing methods, and presents current applications. The authors offer an appraisal of the future direction and impact this technology will have on laboratory settings as 3D printers become more accessible.

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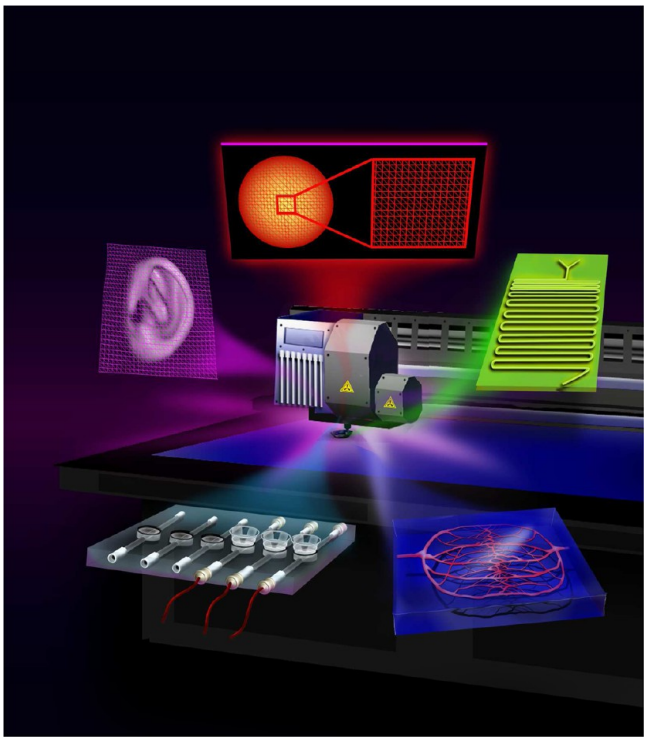

Robert Gates

HISTORICAL PERSPECTIVE

The conception of 3D printing, also referred to as additive manufacturing (AM), rapid prototyping (RP), or solid-freeform technology (SFF), was developed by Charles Hull. With a B.S. in engineering physics from the University of Colorado, Hull started work on fabricating plastic devices from photopolymers in the early 1980s at Ultra Violet Products in California.[1] The lengthy fabrication process (1−2 months) coupled with the high probability of design imperfections, thereby, requiring several iterations to perfect, provided Hull with the motivation to improve current methods in prototype development. In 1986, Hull obtained the patent for stereolithography[2] and would go on to acquire countless more patents on the technology,[3] including, but not limited to, those cited in this article. In 1986, he established 3D Systems and developed the .STL file format, which would "complete the electronic 'handshake' from computer aided design (CAD) software and transmit files for the printing of 3D objects."[4] Hull and 3D Systems continued to develop the first 3D printer termed the "Stereolithography Apparatus" as well as the first commercial 3D printer available to the general public, the SLA-250. With Hull's work, in addition to the development and subsequent patenting of fused deposition modeling (FDM) by Scott Crump[5] at Stratasys in 1990, 3D printing was poised to revolutionize manufacturing and research.

MIT professors Michael Cima and Emanuel Sachs patented the first apparatus termed "3D printer" in 1993 to print plastic, metal, and ceramic parts.[6] Many other companies have developed 3D printers for commercial applications, such as DTM Corporation and Z Corporation (which merged with 3D Systems), and Solidscape and Objet Geometries (which merged with Stratasys). Others include Helisys, Organovo, a company that prints objects from living human tissue, and Ultimaker. Open source options such as RepRap, a desktop 3D printer capable of replicating the majority of its own parts, have been available since 2008.[7]

3D printing technology has found industrial applications in the automotive and aerospace industries for printing prototypes of car and airplane parts, in the architectural world for printing structural models, and in the consumer goods industry for prototype development for companies like Trek and Black and Decker.[8] The applications of 3D printing in private and government defense have been rapidly recognized. For example, applications in gun prototyping and manufacturing processes for the military have already been established. Medical applications of 3D printing date back to the early 2000s, with the production of dental implants and prosthetics.[9] Applications in the food industry,[10] as well as in fashion,[11] have also emerged.

With regard to research settings, 3D printing has been limited to biomedical applications and engineering, although it shows tremendous potential in the chemical sciences. This feature aims to present and compare the basic printing methods available and discuss some of the current work in chemistry as well as in other research and teaching efforts that utilize 3D printing technology.

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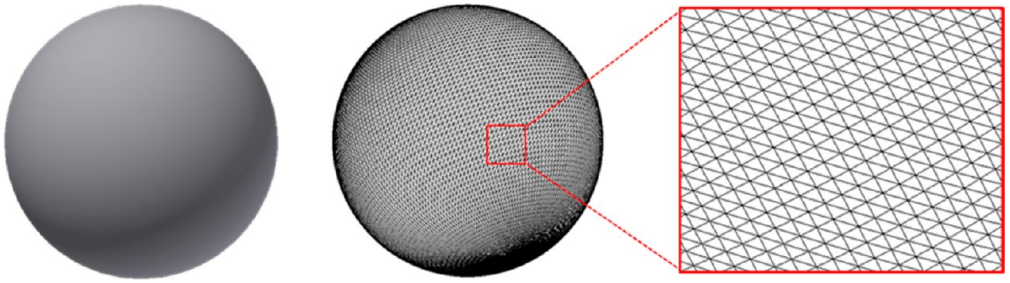

Figure 1. Graphic representation of information in an .STL file. The object, shown on the left, was created in a CAD program and was subsequently saved as an .STL file. The graphical information displayed in the .STL file is shown on the right for the same object. Notice that the surface of the object is triangulated. The spatial coordinates of the triangle vertices are stored in the .STL file, and that information is transmitted to the printer for fabrication.

3D PRINTING METHODS

Overview and .STL Format. 3D printing is utilized for the rapid prototyping of 3D models originally generated by a computer aided design (CAD) program, e.g., AutoDesk, AutoCAD, SolidWorks, or Creo Parametric. The original design is drafted in a CAD program, where it is then converted to an .STL (Standard Tessellation Language or STereo-Lithography) file. The .STL file format, developed by Hull at 3D systems, has been accepted as the gold standard for data transfer between the CAD software and a 3D printer. The .STL file stores the information for each surface of the 3D model in the form of triangulated sections, where the coordinates of the vertices are defined in a text file.[12] By increasing the number of triangles that define a surface, more data points exist in the text file to spatially define the part surface. This increase in vertices results in an increased resolution of the printed device. A visual example of how an .STL file triangulates the defined surfaces can be seen in Figure 1.

The 3D printer interprets the digitally supplied coordinates derived from the .STL file by converting the file into a G-file via slicer software present in the 3D printer. The G-file divides the 3D .STL file into a sequence of two-dimensional (2D) horizontal cross sections (25−100 μm, depending on the fabrication technique),[13] which allows the 3D object to be printed, starting at the base, in consecutive layers of the desired material, essentially constructing the model from a series of 2D layers derived from the original CAD file.[14,15] Development of better slicing algorithms to improve the finished product characteristics is an active area in engineering research.[16]

In the medical field, several other methods are utilized to generate 3D object renderings, e.g., computerized tomography (CT), laser scanning, and magnetic resonance imaging (MRI), which generate data that can all be converted to the .STL format. When merging this digital scanning technology with 3D printing, physicians are able to model the digital images obtained through CTs or MRIs by utilizing CAD software to create an .STL file and subsequently an exact replica of the original scan is printed.[17]

There is an assortment of 3D printing techniques ranging from well-established methods, which have been employed in industrial settings for years, to more recent techniques under development in research laboratories that are used for more specific applications. In the next section, we will expand on five of the more pertinent systems: stereolithography (3D systems), inkjet printing (Z Corporation), selective laser sintering (EOS GmbH), fused deposition modeling (Stratasys), and laminate object manufacturing (Cubic Technologies).

Stereolithography (SLA). Developed by Chuck Hull at 3D Systems,[2] SLA was the first commercialized rapid prototyping method. There are several different approaches to SLA,[13,18−20] including direct/laser writing (Figure 2A) and mask-based

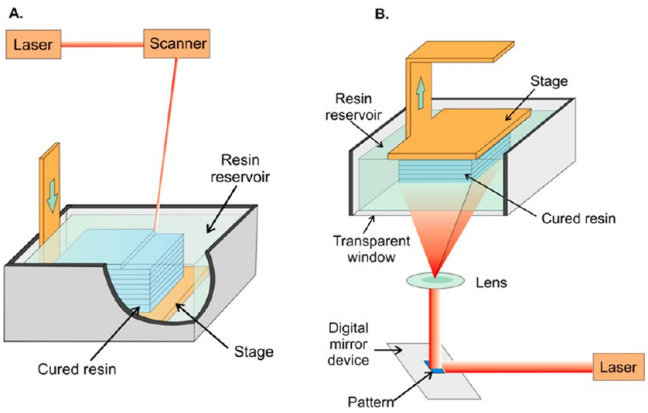

Figure 2. (A) Schematic of a bath configuration SLA printer with a direct write curing process. The stage is located just below the surface of the liquid resin. A single laser moves along the surface of the resin, row by row, until completely curing the desired layer. To initiate the following layer, the stage sinks lower into the vat until a new layer of liquid resin covers the surface and the curing process repeats. (B) Schematic of a layer configuration SLA printer with a projection based curing method. In this particular configuration of an SLA printer, the stage is submerged a defined distance into the photopolymer reservoir. Next, a laser is guided to the stage to polymerize the material in the reservoir that is between the laser and the stage. In the projection based curing method, the digital mirror device allows for a whole layer to be cured simultaneously. The stage can then be raised again by a defined distance, and another layer can be cured. This procedure repeats until the object is printed.

writing (Figure 2B, digital light projection).[20,21] The various approaches can be broken up into a free surface (Figure 2A, bath configuration)[22,23] or constrained surface technique (Figure 2B, layer configuration)[24−26] depending on the orientation of the laser source. The direct/laser writing technique contains the common components of a movable base, a tank of liquid resin, a UV light beam, and a computer interface. The mask-based writing also contains the movable platform, resin vat, computer, and UV beam as well as a "mask" in the form of a digital mirror device (DMD) that allows for the curing of a single layer at once.

In the bath configuration, the UV beam traces a 2D cross section onto a base submerged in a tank of liquid photoactive resin that polymerizes upon illumination. The thickness of the

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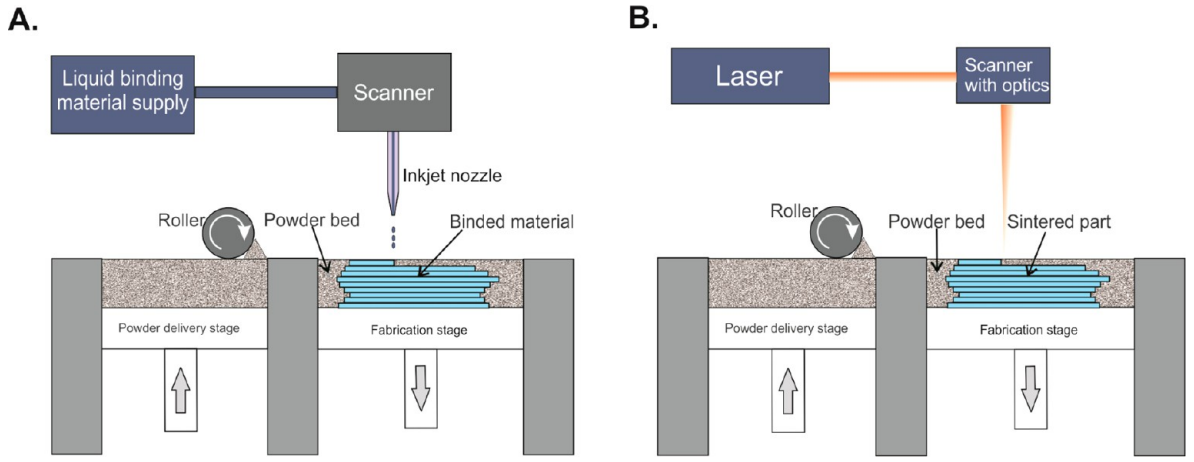

Figure 3. (A) Schematic of an inkjet printing apparatus. For this printing process, the fabrication stage is lowered a defined distance from its initial level. Then, the powder material that will form the device is leveled onto the stage with a roller. An inkjet printing head then prints liquid binding material onto the powder to form one layer of the object. The stage lowers a defined distance again, and the process repeats. (B) Schematic of an SLS 3D printer. The printing steps in SLS are nearly identical to that in inkjet printing, i.e., the stage lowers a defined distance and powder is rolled onto the stage. However, in SLS, a guided laser sinters the material to form the object.

cured resin is dependent upon such factors as duration of exposure, scan speed, and intensity of the power source, all of which depend on the energy of the UV light. After completion of the 2D cross section, the base lowers further into the resin by a predefined distance, and the UV beam begins the addition of the next layer, which is polymerized on top of the previous layer. In between layers, a blade loaded with resin levels the surface of the resin to ensure a uniform layer of liquid prior to another round of UV light exposure. This process is repeated, slice by slice, until the 3D object is completed. The bath configuration is the oldest technique for SLA,[2] and drawbacks include the size of the vat restricting the height of the desired object, resin waste, and extensive cleaning procedures, making the layer configuration an attractive alternative.[22,23]

The layer configuration requires the same components as the bath configuration. However, the movable platform is suspended above the resin reservoir, in contrast to the bath configuration where it is submerged. The light source is located beneath the vat, which has an optically clear bottom. The change in setup requires lower volumes of resin, and the height of the printed part is unrestricted. A thin layer of resin fills a reservoir where it comes in contact with the movable platform. After the initial layer cures, the platform raises, with uncured resin filling the gaps left from the cured layer. If the resin has a high viscosity, the filling step can become quite tedious. The previous steps are repeated until the device is completed (with minimal cleaning stages in comparison to those of the bath configuration).[24−26]

In both configurations, a post fabrication step, using a UV light to guarantee all reactive groups of the resin are polymerized, is required to strengthen the bonding in the final 3D object.[27,28] The direct laser writing method, while able to generate detailed 3D objects, is time-consuming. The mask-based approach uses the same fundamentals as the aforementioned direct/laser writing, but in a high throughput application where a DMD employs millions of mirrors that can be simultaneously controlled. The specific control of the mirrors allows an entire layer to be cured at once, greatly reducing layer production time.[18,20] The thickness of the cured layer (C_D) can be expressed by the following equation:

$$C_D = D_P \ln(E/E_C)$$

The intensity of the light source (E), the critical energy of the resin (E_C), and the depth of light penetration (D_P) are all key aspects that define the cured layer.[20,29] It is important to optimize the layer thickness to increase the curing efficiency, and this information can also be utilized to guide resin choice based on critical energies. The vertical resolution, which is dependent on the cured layer thickness, has been reported at submicrometer to single-digit micrometer resolution, and the lateral resolution depends directly upon the diameter of the UV beam (80−250 μm).[18,22,27,30]

The choice of UV light source varies depending on the resin, but common sources include the HeCd laser (325 nm)[18,25] and the xenon lamp.[26] Two photon polymerization has also been used in SLA fabrication to reach higher resolutions of final printed objects.[31] Resins are one of the main limitations of SLA, not only due to the cost associated with the resin but also due to the fact that only one resin can be used in the printing process at a time, thus limiting overall device design. Resins are limited to either epoxy or acrylic bases, and the majority of these materials are brittle and can shrink upon polymerization.[13,27] SLA 3D printers are traditionally expensive, but high resolution (25 μm layers) and efficient (1.5 cm/h building speed) desktop models are becoming more accessible to laboratories and even personal homes.[32]

Inkjet Printing. The concept of inkjet printing was initially described in 1878 by Lord Rayleigh,[33] and in 1951, Siemens patented the first two-dimensional (2D) inkjet type printer called a Rayleigh break-up inkjet device.[34] Since its advent, inkjet printing has served much use in commercial industry, mostly for printing inks on paper. However, as far back as 2001, inkjet printing has also been used for printing structures out of sol−gel, conductive polymers, ceramic, metal, and nucleic acid or protein materials, as described in reviews.[35]

The two main types of inkjet printing are continuous and drop-on-demand (DOD). The continuous inkjet printing technique, which was developed by Sweet at Stanford University in the mid 1960s, requires electrostatic plates in the printer head to direct ink droplets onto paper for printing or into a waste compartment to be recycled and reused.[36] The

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droplet size and spacing are controlled by application of a pressure wave pattern. In the DOD technique (Figure 3A), which was pioneered by Zoltan[37] and Kyser and Sears,[38] a voltage and pressure pulse directs the ink droplet, eliminating the need for the separation of waste ink from the printer head. Since the advent of the two main inkjet printing methods, there has been significant development of new printing techniques in both categories.

3D inkjet printing is mainly a powder-based method where layers of solid particles, typically 200 μm in height with particle sizes ranging between 50 and 100 μm,[39] are bound together by a printed liquid material to generate a 3D model. Specifically, a first layer of powder is distributed evenly on the top of a support stage, e.g., by a roller, after which an inkjet printer head prints droplets of liquid binding material onto the powder layer at desired areas of solidification. After the first layer is completed, the stage drops and a second powder layer is distributed and selectively combined with printed binding material. These steps are repeated until a 3D model is generated, after which the model is usually heat-treated to enhance the binding of the powders at desired regions. Unbound powder serves as support material during the process and is removed after fabrication.

As a powder-based 3D printing technique, inkjet printing does not require photopolymerizable materials or liquids with modified viscosities. Powders from polymer, ceramic, or glass materials can be combined with liquid binding materials to generate a 3D model,[40] which has significantly expanded the technique's application in areas like art design and industrial modeling.[41] Biological scaffold fabrication,[42] which will be discussed in more detail in later sections particularly with respect to drug delivery studies, was impacted by the aforementioned technique. However, one caveat for the method is that the printed liquid's chemical and physical properties will dominate those of the printed device. For example, many polymer glues are biologically toxic and thus cannot be used for tissue scaffold fabrication.[43] Another limitation of inkjet printing is the optical transparency of finished devices; incomplete interaction of binding liquid with powder particles can cause a material to have reduced transparency due to light scattering, which would be a severe limitation for microscopy studies. Unbound particles can also result in significant porosity of finished materials and surface roughness, which, depending on the application, can be an advantage or limitation. However, nonpowder based (usually polymer-based) inkjet methods do exist,[44] e.g., Stratasys PolyJet technology, which can print 16 μm photopolymer layers.[45]

Selective Laser Sintering (SLS). Developed by Carl Deckard and Joseph Beaman in the Mechanical Engineering Department at the University of Texas-Austin in the mid-1980s,[46] SLS is another powder-based 3D model fabrication method. Although SLS is similar to inkjet printing (Figure 3), SLS uses a high power laser, e.g, CO_2 and Nd:YAG,[47] to sinter polymer powders to generate a 3D model, rather than using liquid binding materials to glue powder particles together. In the SLS process, a first layer of powder is distributed evenly onto a stage by a roller and is then heated to a temperature just below the powder's melting point. Following the cross-sectional profiles designated in the .STL file, a laser beam is selectively scanned over the powder to raise the local temperature to the powder's melting point to fuse powder particles together. After the first layer is completed, a second layer of powder is added, leveled, and sintered in the desired areas. These steps are repeated to create a 3D model. The powders that are not sintered by the laser serve as support material during the process and are removed after fabrication. Figure 3B provides a schematic of the process of SLS. A more detailed discussion of SLS basics such as laser types and binding mechanisms can be found in the literature.[47,48]

One advantage of SLS is that a wide range of materials can be used, from polymers such as polycarbonate (PC), polyvinyl chloride (PVC), acrylonitrile butadiene styrene (ABS), nylon, resin, and polyester[49] to metal and ceramic powders.[50,51] Also, a binding liquid material is not required in SLS. However, SLS printed models suffer shrinkage or deformation due to thermal heating from the laser and subsequent cooling, which has been under investigation in the literature for some time.[52] Achievable resolutions in SLS techniques are dependent on multiple parameters including laser power and focusing as well as the size of the powder material. Work is ongoing to push fabricated feature sizes using SLS below that of inkjet printing techniques, roughly below 50 μm.[50,53]

Fused Deposition Modeling (FDM). Developed by Scott Crump of Stratasys, FDM is one of the most widely used manufacturing technologies for rapid prototyping today. FDM fabricates a 3D model by extruding thermoplastic materials and depositing the semimolten materials onto a stage layer by layer.[15,40,54] As shown in the schematic process in Figure 4,

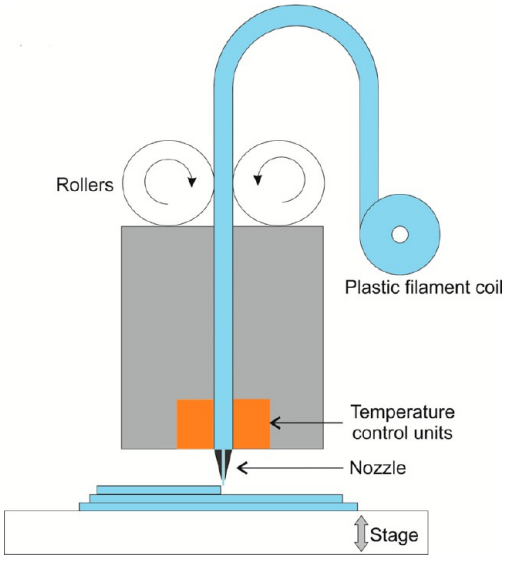

Figure 4. Schematic of an FDM 3D printer. In this method, plastic filament is directed into a heating block where it is heated to a semimolten state. The molten material can be printed onto an adjustable stage to form a layer of the desired object. The stage is adjusted (lowered) and another semimolten layer is printed.

thermoplastic filaments, the material used to build 3D models, are moved by two rollers down to the nozzle tip of the extruder of a print head, where they are heated by temperature control units to a semimolten state. As the print head traces the design of each defined cross-sectional layer horizontally, the semimolten materials are extruded out of the nozzle and solidified in the desired areas. The stage then lowers and another layer is deposited in the same way. These steps are repeated to fabricate a 3D structure in a layer-by-layer manner. The outline of the part is usually printed first, with the internal structures (2D plane) printed layer by layer. Surface defects from this particular process include staircase and chordal effects resulting

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from the nature of the slicing software and .STL file format. Internal defects can result from heterogeneities in the filament feed diameter and density, as these can effect how the material is extruded from the printer nozzle.[55]

A notable advantage of FDM is that it can create objects fabricated from multiple material types by printing and subsequently changing the print material, which enables more user control over device fabrication for experimental use. Besides conventional materials such as PC, polystyrene (PS), and ABS, FDM can also print 3D models out of glass reinforced polymers,[56] metal,[57,58] ceramics,[57,59] and bioresorbable materials.[60] However, a binder is typically mixed with ceramic or metal powders, enabling the material to be used in a filament form.[57]

Laminated Object Manufacturing (LOM). LOM, developed by Helisys,[61] generates a 3D model by stacking layers of defined sheet materials such as paper, plastic, and metal.[49] As shown in the schematics in Figure 5, after the first layer of a sheet material is loaded onto a stage, a laser (CO_2 lasers have been used[62]) or razor traces the designed cross-section to define the pattern on the layer.[63] After the excess material of the sheet is removed, a second layer covers the previous layer and the laser or knife tracing will define the next pattern based on information in the .STL file. Adjacent layers are combined by use of adhesives or welding,[64] e.g., for paper or metal, respectively. These steps are repeated to generate a layered 3D model.

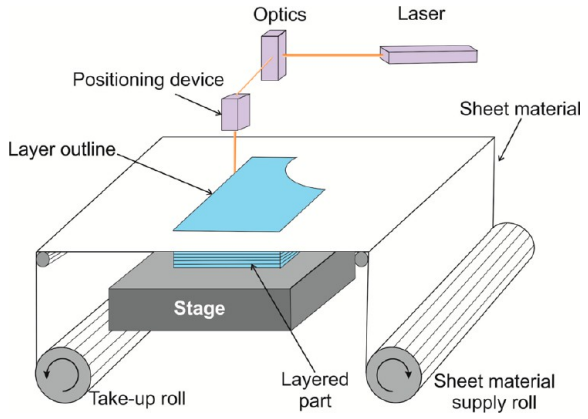

Figure 5. Schematic of an LOM 3D printer. A sheet of material to form the object is rolled over the stage, and a laser (shown here) or a razor can trace the outline of the desired object. The excess material is removed, the stage is adjusted, and another layer of material is rolled over the stage. Each layer is secured to the previous by an adhesive in the case of paper or by welding when metals are employed as the material.

The LOM process does require a heating step during production, either on the support stage or on the roller, to ensure that the adhesive acts to bond the sheets together. The effects of this step on the nonuniformities in the fabricated part are, in general, minimal compared to defects that arise in other techniques, such as FDM.[65] However, if the local temperature of either the roller or the stage is not controlled well enough, the part could become delaminated due to inefficient adhesive heating or the part can suffer structural damage if the temperature is high enough to damage the adhesive.[66] Another limitation of LOM is that the materials applicable for method use are limited by their ability to be formed into sheets and to be integrated with adhesive.

Each additive manufacturing technique described above has its own limitations and advantages in producing prototype models. For a better understanding, numerous comparisons of these rapid prototyping techniques have been reported in detail.[40,67] Table 1 addresses the principle, materials, solvent compatibility, resolution, cost, and applications associated with the five 3D printing techniques discussed above.

Solvent compatibility for 3D printer materials is still under exploration; however, polymer reactivity, as well as the other mentioned materials' reactivities, with aqueous and organic solvents are generally known and well documented. It is anticipated that as techniques and materials become more popular in the chemical and biochemical community, solvent compatibility will become less of a variable in such studies. In the methods that require a laser, resolution is determined not only by the laser spot size but also by the physical properties of the materials that govern the polymerization (SLA) or the thermal heating and cooling (SLS and LOM). Resolutions in the other mentioned techniques are limited by a material's cooling properties (FDM), viscosity, and nozzle diameter. Printer costs were obtained by contacting the listed company for quotes, and printer brand name and model name are provided, if possible. Desktop printers that may be lacking in terms of resolution are generally <$10,000 while midtier printers can cost up to $100,000. Printers for industrial use, high resolution, or for high throughput printing can cost $250,000 or more. These price points are estimates of the market prices.

CURRENT APPLICATIONS

The assortment of topics that follows is not meant to be an inclusive list on the full applications of 3D printing technology. Rather, it aims to give the reader an appreciation for the potential 3D printing has in an array of disciplines. Specifically, the topics to be discussed are the applications of rapid prototyping in biomedical engineering, pharmacokinetics/pharmacodynamics, forensic science, education, micro/macrofluidics, electronics, scaling (industry), and customizable labware.

Biological Applications. *Biomedical Engineering. Tissue Scaffolding.* Additive manufacturing has found widespread use as a tool to bioengineer tissue, varying in composition from bone and teeth to vascular and organ scaffolding. Major concerns when introducing a foreign scaffold to the body are the ability of the material to be absorbed by the body (bioresorption) and whether or not it will be rejected by the body (biocompatibility). For these reasons, scaffolds are traditionally comprised of tissue taken from the individual in need (autogenous tissue). However, in some cases the required scaffold area is large enough that autogenous tissue sampling is not feasible for the patient. The ability to customize a 3D printed scaffold for tissue regeneration allows for individualized treatment while avoiding the need to sample from the patient's own tissue for scaffold formation. In this respect, 3D printing has become an attractive avenue for the development of biocompatible materials that are resorbable.[68,69] Electrospinning is one of several fabrication methods that have been conventionally used for bone scaffold materials and is capable of fabricating bone replicate fibers that are submicrometer to nanometer in diameter. This fabrication technique relies on a high voltage power supply to electrospray a polymer feed solution containing nanoparticles of bone substitute from a nozzle onto a conductive rotating drum. Limitations with this

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Table 1. Comparison of 3D Printing Methods

method	principle	materials	solvent compatibility	resolution (XY/Z) (μm) [ref]	cost (USD)	applications [ref]
SLA	UV initiated curing of defined photoresin layers	Epoxy or acrylate based resins with proprietary photoinitiators, support material is mix of propy-lene/polyethylene glycols, glycerin, and/or acrylate	Most polymer materials can absorb small organic molecules and can absorb organic or aqueous solvents resulting in swelling of the bulk material	70−250/1−10, <1 with two photon polymerization; refs 13, 26, 31, 130	Formlabs Forml 3 299; 3D Systems ProX 950: >500 000	refs 13, 22, 136
Inkjet	Powder-liquid binding; Polyjet technology (hybrid between SLA and Inkjet) allows inkjet printing of photoresins	Photoresins or more commonly, plaster powder particles (50−100 μm in diameter)	Most polymer materials can absorb small organic molecules and can absorb organic or aqueous solvents resulting in swelling of the bulk material	20−50/50; refs 35, 131	3D Systems Zcorp Zprinter 150: 16 580, 650: 59 000, 850: 93 000; Stratasys (polyjet) Objet 30: 55 660, Objet 24: 19 900	refs 76, 106, 107
SLS	Laser induced heating of powder particles	Powdered PC, PVC, ABS, nylon, resin, polyester, metals, ceramic powders	Most polymer materials can absorb small organic molecules and can absorb organic or aqueous solvents resulting in swelling of the bulk material	50/1−2; refs 132−134	3D Systems: 250−450 000	ref 100
FDM	Extrusion of molten thermoplastics	Wax blends, PC, PS, ABS, nylon, metals/ceramics (with binder)	Most polymer materials can absorb small organic molecules and can absorb organic or aqueous solvents resulting in swelling of the bulk material	250/50; refs 15, 89	Stratasys Mojo: 9 900, Dimension: 34 900, UPrint: 20 900; Makerbot Replicator 2 000	refs 15, 137
LOM	Laser/razor cutting of heated, adhesive coated sheet material	Adhesive-coated polymer, paper, cellulose, metal sheets	Paper or cellulose may not be amenable to some chemical applications	10/100; refs 15, 135	Cubic Technologies 14 995	ref 138

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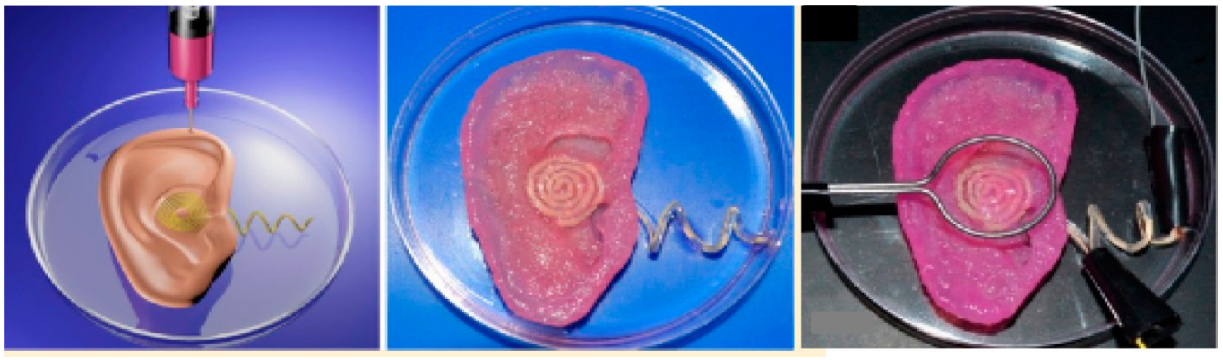

Figure 6. 3D printed bionic ear. Computer schematic of completed bionic ear (left). 3D printed silicon scaffold incorporating chondrocytes and silver nanoparticles for cochlea formation (center). Experimental setup of bionic ear complete with electronic modalities (right). Reprinted from ref 91. Copyright 2013 American Chemical Society.

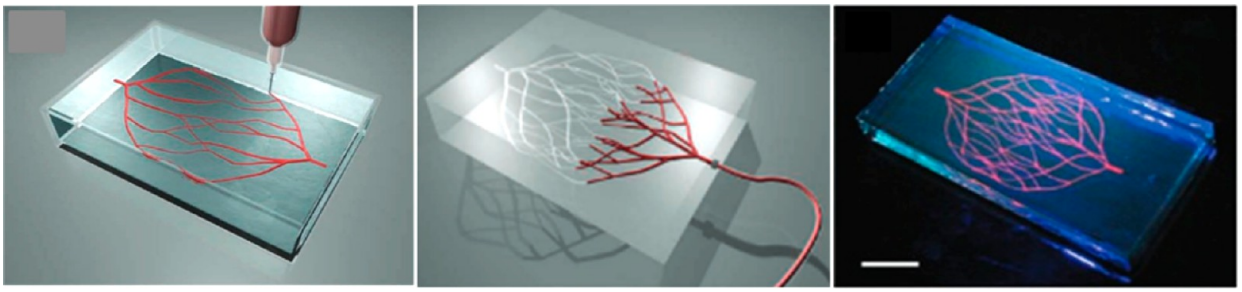

Figure 7. 3D printing technologies used for microvascular formation. Direct printing of fugitive ink into a photocurable gel reservoir (left). Void spaces are filled in with a liquid filler chemically resembling the gel reservoir. After photopolymerization of the filler and gel reservoir, the printed ink is removed by liquification (center). Fluorescent image of red stained fugitive ink in a completed microvasculature device (right). Scale bar = 10 mm. Reprinted with permission from ref 96. Copyright 2011 John Wiley & Sons.

method include the utilization of a high voltage (often >20 kV) as well as lack of control over scaffold geometry and porosity as is encountered with other traditional methods.[70,71]

Autogeneous bone is ideal for bone graphs, as it allows for new bone growth at the implantation site due to already present growth factors. The risk of infection, often seen with foreign implants, is lowered in patients with autogenous grafts.[72] Many bone replicate materials are made from calcium phosphate ceramics (tricalcium phosphate (TCP, $Ca_3(PO_4)_2$), hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), calcium phosphate cements (CPC), monetite ($CaHPO_4$), or brushite ($CaHPO_4 \cdot 2H_2O$)), as these are comparable to the mineral components of bone.[72,73] This is not an exclusive list, however, as new combinations of materials are being tested for increased bioresorption and biocompatibility, such as a β-TCP and bioactive glass mixture.[74] These materials are made into 3D scaffolds by selective laser sintering,[75] inkjet-based printing,[76] or printing the powdered form of the chosen material with an organic binder to form a ceramic 3D scaffold.[77] The porosity of the implant becomes important as implant adhesion to bone occurs through bone ingrowth into the pores of the prosthetic[78] and it facilitates biodegradability of the scaffold due to reduced material presence.[76] Ideal porosity and pore size of the 3D printed scaffold to encourage bone ingrowth have been reported as 30−70% and 500−1000 μm, respectively.[78] However, micro to macroscopic pore sizes ranging from less than 20 μm to 0.5 mm have been reported.[79,80] Each of the bone replicate materials have a different pore size and achievable porosity,[81] and the choice of bone scaffold material depends largely on the purpose of the graft, as the materials used to form 3D grafts have variable resorption times.[72] For example, monetite structures have been found to absorb faster into muscle than brushite.[77] Many articles have outlined fabrication and *in vivo* and/or *in vitro* testing of various bone substitute materials,[76,82,83] with 3D printed materials displaying comparable biocompatibility to commercial bone substitutes.[80]

Soft tissues have previously been fabricated using a number of techniques including thermally induced phase separation.[84] This technique requires a polymer mixed with a solvent to be injected into a glass mold; after several tedious steps (including 3 h in liquid nitrogen, followed by a 7 day incubation in alcohol to remove the solvent, and a day to dry) the scaffold is completed. Traditional techniques for soft tissue fabrication suffer from lengthy protocols and a lack of control with regards to scaffold porosity.[71] Producing synthetic organs for organ transplants is plausible when utilizing 3D tissue engineering. While the technology is still far from achieving this ambitious goal, 3D printing allows for the printing of cells and hydrogels, which are hydrated polymers that provide a biodegradable structure onto which cells can adhere and grow.[85] When using hydrogels for tissue engineering, the scaffold must be biocompatible, retain its structure, and allow for cell adherence and growth.[86] Scaffold dimensions range from μm to mm, with a variety of materials available depending on the desired scaffold strength, porosity, and type of tissue application (soft or hard). Hydrogels are most suited for soft tissues.[87] Ideal porosity composition of scaffolds for tissue engineering has been reported to be between 60 and 80%, with pore sizes ranging from 100 to 500 μm.[88] Reviews by Tsang and Bhatia,[89] Fedorovich et al.,[90] and Yeong et al.[71] highlight 3D tissue engineering techniques available for printing cells and tissue scaffold materials as well as the various compositions that can

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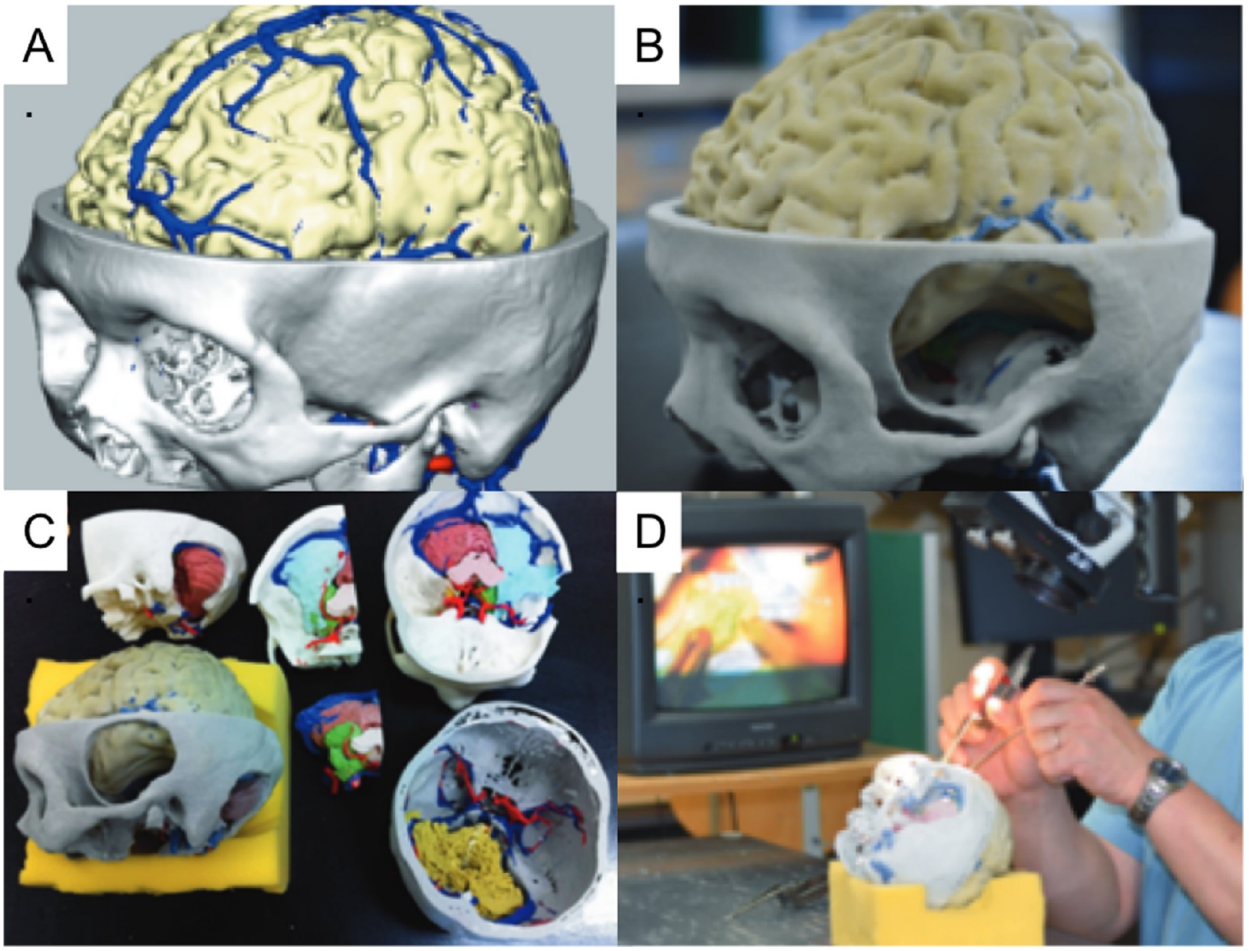

Figure 8. Use of 3D printing for presurgical planning. MRI, CT, magnetic resonance angiography (MRA), and digital subtraction angiography (DSA) were used to create the 3D computer models of the cranial anatomy. SLS was used to print realistic color models of the anatomy for simulating tumor removal. (A) Computer schematic of 3D model obtained from imaging of patient anatomy. (B) Resulting 3D printed plaster model used for simulation. (C) Detailed 3D printed plaster models for surgical simulation. (D) Presurgical performance of procedures on a printed model viewed microscopically. Reprinted with permission from ref 101. Copyright 2013 The Journal of Neurosurgery Publishing Group.

be selected to suit a specific application. Inkjet and direct writing are commonly used 3D printing techniques for soft tissue fabrication and offer a faster completion time than their predecessors.

Examples of hydrogel applications for tissue engineering encompass a vast array of organ and soft tissues. Incorporation of support (silicon), biological (chondrocytes), and electronic (conducting silver nanoparticles) modalities has led to the development of an anatomically correct 3D printed bionic ear (Figure 6) capable of detecting electromagnetic frequencies produced from a stereo.[91] The liver has proven difficult to recreate on a 3D platform due to its complex structure. There are a number of rapid prototyping techniques that lend themselves to the fabrication of bioartificial livers, each with their own advantages and disadvantages.[92] Despite the apparent challenges, there are a variety of examples where hepatocytes were successfully integrated into a 3D printed scaffold.[93,94] With the number of diseases that affect the cardiovascular system, it is appropriate to apply tissue engineering for vasculature reconstruction. This has been accomplished using a variety of rapid prototyping techniques and materials, from designs as simple as a single channel,[95] to designs that recreate the complex geometries of vascular pathways,[96] and even scaffolds based off complex collagen forms.[97] Figure 7 shows an example of intricate microvascular construction using 3D printing.

Surgical Preparation. 3D printing has facilitated advancement in individualized patient care, allowing for development of patient specific treatment plans via the printing of patient anatomy. Having a tangible model of the patient's anatomy that can be studied before surgery serves to better prepare physicians than relying solely on 3D images acquired by MRI or CT scans, which are viewed on a flat screen.[68] Furthermore, having an exact replica of the anatomy allows for medical procedures to be simulated beforehand. Although still in a mostly exploratory stage, there have already been numerous cases where 3D printed models have been used to gain insight into a patient's specific anatomy prior to performing a medical procedure. Namely, this methodology has been applied in recreating a calcified aorta with 3D printing to develop a procedure for plaque removal presurgery,[98] using a 3D model of bone growths on a shoulder to aid in surgical organization of their removal,[99] constructing a premature infant's airway to study aerosol drug delivery to the lungs,[100] and simulating presurgical tumor removal from a skull and deep tissue, as seen in Figure 8.[101]

Pharmacokinetics/Pharmacodynamics. Inkjet-based 3D printing has been used extensively in the fabrication of drug

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delivery devices, as it allows for more control of the design and fabrication of implants that can be used for direct treatment. Traditional systemic treatment of localized infections affects the intended site as well as nonafflicted tissues. In many cases, such as the treatment of bone infections, it is advantageous to have direct treatment without unnecessary widespread effects. 3D printed drug implants are fabricated via the printing of binder (a solution that is able to solubilize the chosen powder) onto a matrix powder bed, facilitating controlled drug release by providing a barrier between tissue and drug, or printing of binder onto a powder bed of drug in an additive manner, resulting in layers that are typically 200 μm thick.[102,103] In this manner, a number of different drug delivery devices have been designed that allow for various drug release profiles. Additive manufacturing technology has been used to fabricate drug delivery devices that are more porous than their compression-based counterparts and can incorporate powdered drugs,[104] allowing for faster drug release. These devices can be made in a number of complex geometries,[103] with multiple drugs loaded throughout a device, surrounded by barrier layers that modulate drug release.[102,105] Traditional compression fabricated devices are made from a homogeneous mixture of support material and drug and are restrained to a continuous and singular drug release profile.[106] For these reasons, 3D printed drug implants offer several advantages over traditional fabrication methods and have been successfully used in animal models showing localized drug dispersion.[102]

Forensic Science. 3D printing has had a meaningful impact on medical imaging in the field of forensic science, allowing for anatomically correct recreation of bodily injuries from CT and MRI scans. For example, models of both internal and external wounds have been recreated that allow for better explanation of forensic findings, while avoiding the need to present disturbing evidence in the presence of victims' relatives.[107] 3D printing techniques were used to recreate skull fragments from a blunt force head injury and aid in weapon identification and determination of the mechanism of injury leading to death.[108] A similar use of 3D printing saw the recreation of a skull after a traumatic injury to deduce the cause of injury, with results comparable to those achieved using traditional methods to isolate bone from the victim.[109] Forensic assessment of a deformed skull from the 18th century yielded a facial reconstruction based on a 3D printed version of the skull, from which authors inferred the cause of deformation.[110]

Education. The educational applications of 3D printing extend beyond the study of anatomically correct models of body parts in healthy and diseased states.[111] As the technology becomes more affordable, its use in educational settings is more commonplace. Recently, a model of a polypeptide chain has been fabricated using 3D printing and is able to mimic folding into secondary structures due to incorporation of bond rotational barriers and degrees of freedom considerations.[112] Such a model could greatly aid in students' ability to comprehend peptide structure, and the application need not be limited to biomacromolecules. Studies have led to the conclusion that students were better able to conceptualize biomolecular structures when using 3D models, as confirmed by administering pre- and postcomprehension tests.[113,114]

Chemical Applications. *Micro/Macrofluidics.* 3D printing stands to have a substantial impact on the field of microfluidics and lab on a chip technology. While the possible functions of 3D printed microfluidic devices are far reaching, utilization of 3D printing for bioanalytical research seems a likely extension of previous efforts made with 3D environments to control cell patterning using soft lithography.[115] And while soft lithography has proven successful for this purpose, as noted in a review by Kane et al.,[116] there are many benefits to moving to a 3D printed regime. Compared to the lithographic techniques typically employed by many educational laboratories, ours not excluded, 3D printing offers a much simpler fabrication process by foregoing the need to use a master for replica molding.[117] What has made soft lithography-based PDMS microfluidic devices attractive as a rapid prototyping tool lies in the user's ability to fine-tune the device easily until the desired effect is achieved, all within a short period of time. Rightly so, the comparison of 3D printing to standard microfluidic fabrication techniques as well as the merger of the two has already been made by Rapp et al.[117] While traditional techniques have their value, 3D printing may be the answer to some of the troubles that have plagued traditional replica molding techniques, including a lack of standardization between laboratories and the labor-intensive fabrication processes.

The fabrication of a complex microvascular network composed of 100−300 μm cylindrical channels capable of diffusion-based mixing under laminar flow profiles as well as mixing from turbulent flow is one of the earliest examples of 3D printing for microfluidic applications.[118] The microvascular scaffold was fabricated layer-by-layer on a moving stage using robotic deposition of a fugitive organic ink, a process known as direct writing. Overall, a 16-layer scaffold could be formed in under 3 min. Afterward, ambient-curing clear epoxy resin was introduced as a support material for the scaffold. The fugitive organic ink that denotes the space for the microchannels is removed from the cured epoxy by heating at 60 °C under a vacuum, leaving interconnected channels with root-mean-square surface roughness on the order of tens of nanometers. In order to form isolated complex connections between microchannel layers, a photocurable epoxy was selectively introduced to areas of the scaffold. Using a mask to selectively cure portions of the epoxy following UV exposure, mixing channels that spanned several layers of the scaffold were formed. The extent of mixing between a red and green fluorescent dye, when introduced at two different areas of the device, was quantified by measuring average yellow intensity across a mixing channel versus the complete mixing of the two dyes off channel. Flow rates of 0.1−45 mL/h were employed during the study. Previous efforts at 3D microfluidic devices were made from layering sections created from conventional lithographic techniques. While this example draws on a combination of lithographic and 3D techniques, it serves as a prime example of where 3D printing in microfluidic-based microvascular mimics started.

The Cronin group fabricated a 3D printed reaction device (0.65 mL total volume) for flow-based organic synthesis that has been directly paired via connectors with electrospray ionization mass spectrometry for the characterization of small amounts of synthesized organic products. The device was made from chemically inert polypropylene using an FDM 3D printer. Device dimensions were 46.5 mm × 80 mm, and the internal feature diameter was 1.5 mm. The device employed reaction flow rates varying from 62.5 to 312.5 μL/min during synthesis.[119] Another polypropylene device used for organic synthesis printed via FDM coming from the Cronin group weighs 3.9 g with dimensions of 25 mm × 50 mm × 3 mm. It consists of a reaction chamber, cylindrical channels 0.8 mm in diameter, and has a total reaction volume of 60 μL. With this

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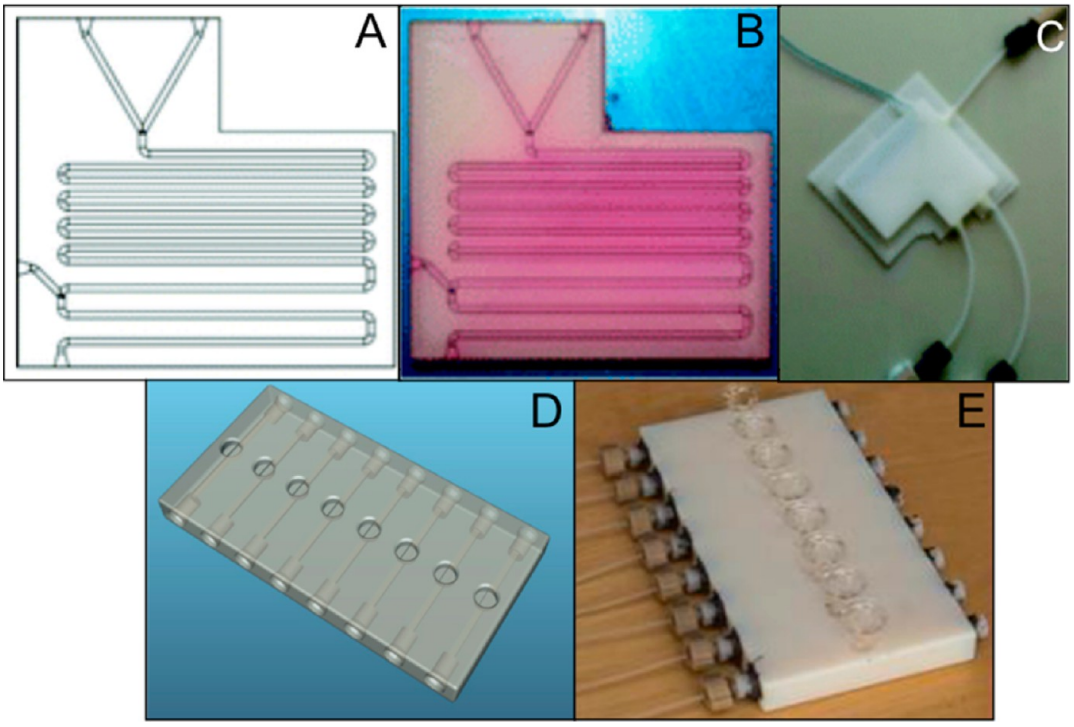

Figure 9. 3D printed fluidic devices. (Top panel) (A) Design schematic before printing . (B) Printed organic reactionware device (total volume of 270 μL) with channels stained for visualization purposes. (C) Completed device including connectors for sample introduction. Reprinted with permission from ref 120. Copyright 2012 Royal Society of Chemistry. (Bottom panel) (D) Computer rendering of macrofluidic device. (E) Printed device incorporating connectors for fluid flow through internal channels and membrane inserts on top of the device. Reprinted from ref 121. Copyright 2013 American Chemical Society.

device, imine formation from a reaction of benzaldehyde and benzylamine was characterized based on flow rates in the reaction vessel ranging from 10 to 200 μL/min. A benefit to these organic reactionware devices is that they can be fabricated in a few hours, are reusable, and due to the millimeter scale of the devices, can avoid blockages from formed products.[120] Examples of 3D printed reactionware for organic synthesis can be seen in Figure 9A−C.

Recently, work has been published by the Spence group on the utilization of 3D printing to develop a multiple channel device (1.5 mm deep and 3 mm wide channels) with integrated connectors and membrane inserts, for the purpose of monitoring drug transport through the device, capable of affecting cells cultured on the inserts. This device, fabricated using a polyjet-based printer, is reusable and is capable of high-throughput studies with eight parallel channels. It integrates with commercially available parts and syringe pumps for ease of construction and sample delivery. For drug transport studies, two antibiotics ranging in concentrations from 100 to 2000 nM were flowed in a channel underneath a cell culture insert at 1 μL/min and were subsequently sampled from the insert for analysis using mass spectrometry. Cell viability on the device was confirmed by application of a dead cell stain to endothelial cells after flowing saponin in the channel underneath the cell culture insert containing the confluent layer of endothelial cells.[121] Figure 9D−E shows the 3D printed fluidic device used for these studies.

Using stereolithography, an electrochemical flow cell has been fabricated that can be integrated with electrodes without the use of adhesives. The dimensions of the channel in the cell were 3 mm in width by 3.5 mm in length and either 190 or 250 μm in height. Flow rates up to 64 mL/min were employed without leaking. To characterize mass transport in the flow cell, the oxidation of ferrocenylmethyl trimethylammonium hexaflorophosphate was monitored using a two-electrode setup with a working electrode of either gold or a polycrystalline boron-doped diamond band and a quasi-reference electrode of a silver chloride coated silver wire. Such a device has potential impact on future analytical and kinetic based flow measurements.[122]

Electronics. There are vast applications concerning the integration of 3D printing and electronics, and while this partnership is still in its infancy, the foundation that has been laid thus far is promising for future endeavors. A lithium ion battery has been 3D printed with implications in energy storage.[123] 3D printing technology has been used to fabricate a usable electrochemical cell.[124] A prototype of an electrically conductive model was made by 3D printing a plaster-based structure that contained carbon nanofibers.[125] Precise inkjet-based 3D printing of conductive copper has been achieved, with low costs and low material waste, and has applications in directly applying conductive material for circuit board production. Traditional methods to fabricate circuitry rely on lithographic technology which is time-consuming and expensive due to the many steps involved.[126] Current electroencephalography (EEG) and electrocardiography (ECG) technologies rely on a Ag/AgCl electrode that suffers from several drawbacks, including the use of gel to lower impedance between the electrode and skin and the possibility of skin lesions. Dry electrodes bypass these drawbacks, and recently a 3D printed dry electrode has been fabricated with gold spin-coated on the surface. Results are comparable to standard wet Ag/AgCl electrode models.[127]

Scaling. Additive manufacturing techniques have been used for industrial prototyping in the past, but when it comes to

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large-scale prototyping and fabrication, traditional methods such as hot embossing and injection molding are preferable methods. A benefit 3D printing has over these more traditional methods is that 3D printing-based prototyping does not require the fabrication and use of a mold from which all others will be based.[117] Instead, the "master" for 3D printing is the .STL file. However for small-scale or scalable applications, 3D printing would be an ideal rapid fabrication technique given the array of available materials that can be printed and time saved due to not having a physical master for rapid prototyping.

Custom Labware. Rapid prototyping has practical applications in the fabrication of everyday or custom labware. Having the luxury of easily acquiring a necessary piece of equipment through rapid prototyping has far reaching applications for the general lab and has been applied to the creation of custom organic chemistry reaction vessels.[124,128] In some cases, the total volume capacity approaches microliter volumes.[120] Further highlighting the utility of additive manufacturing in this area, a custom 3D printed sample holder was made to aid in the live imaging of tumor cell growth using single plane illumination microscopy.[129]

FUTURE DIRECTION

Materials. Those developing materials to be utilized for 3D printing must take into account variety, composition, strength, and finishing procedures in order to increase the versatility of the technology. Currently, the variety of materials is limited to the ability of the materials to be powder-based or have low enough viscosities to be extruded from the printing head. Many manufacturers require proprietary materials to be used in their 3D printers or risk forfeiting the warranty. This scenario has limited the material pool, and thus, for 3D printing to continue to grow, the quantity and diversity of materials must increase. Research for the development of 3D printing materials has a plethora of opportunities. Including synthesis and discovery of new or mixed material compositions that are amenable to printing techniques, new methods of printing to increase speed while simultaneously reaching higher resolutions, and materials on par with the strengths of materials machined by conventional methods. Another area of growth centers on the need for postprint processing. More efficient ways to remove support material will prove beneficial, specifically in microfluidics, by allowing smaller details and features, such as channels, to be printed and subsequently cleared of support material. The development of a chemical polish for clear materials would be advantageous for developing optically transparent devices, especially for designs with areas that are difficult to access by conventional polishing methods.

File Sharing. 3D printing offers an unprecedented opportunity for sharing and collaboration between laboratories due to the nature of the digital data files, i.e., .STL files, generated from CAD software during part development. Currently, device fabrication is described in publications, but when a different group aims to fabricate a similar device, they would have to mimic the description in the original paper in their own lab. This process can lead to user error during fabrication based on subtle differences and interpretations. With 3D printing, the .STL file can be shared, whether upon publication of a concept or perhaps in an open scientific database, and an exact replica of the original device can be printed, enabling researchers to share their experimental designs with other researchers throughout academia.

Outlook. The creation of nearly any imaginable geometry can be made tangible using CAD software capable of producing .STL files to be read and fabricated by a 3D printer. Choosing the appropriate printer type, SLA, inkjet, SLS, FDM, or LOM, depends on the design, materials, and purpose of the device. 3D printing has become a useful tool in a number of different fields, and as printer performance, resolution, and available materials have increased, so too have the applications. While this featured article does not present a complete offering of what is possible with 3D printing, it serves to show the platform from which future endeavors will launch. As evidenced by the above-mentioned publications, researchers in chemical and biochemical disciplines are exploring new applications with this technology to improve upon current methods and to facilitate new experimental designs that can expand the types of questions scientists can probe. The authors anticipate that this exciting new technology will lead to new avenues of research with 3D printing at its foundation.

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Notes

The authors declare no competing financial interest.

Biography

Bethany C. Gross graduated from Kalamazoo College in 2010 with a B.A. in chemistry. Currently, her research at Michigan State University encompasses the development of a flow-based 3D printed microfluidic device with integrated electrodes to initiate and evaluate injury-induced blood-clot formation. Jayda L. Erkal graduated from Vanderbilt University with a B.A. in chemistry in 2010. Currently, she is a Ph.D. candidate in the Spence group at Michigan State University, and her research focuses on the development of electrochemical and optical methods for determining the release of red cell metabolites in microfluidic systems. Sarah Y. Lockwood graduated from Saginaw Valley State University in 2010 with a B.S. in chemistry. She is a Ph.D. candidate at Michigan State University, where her research focus has delved into the development of a diffusion-based dynamic *in vitro* system, using soft lithography or more recently 3D printing, to obtain PK/PD profiles, simultaneously, on a single platform. Chengpeng Chen received his bachelor's degree in chemical oceanography from the Ocean University of China. Since joining Michigan State University as a doctoral candidate, he has been developing new enabling technologies using 3D printing for enhanced measurements involving cell to cell communication. Dana Spence is an Associate Professor of Chemistry and Cell and Molecular Biology. His group develops necessary technologies for investigating the role of red cells in human disease based upon these cells' interactions and responses to chemical and physical stimuli.

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