

1 **Current and future scope of 3D printing applications within chemistry, and associated**
2 **pharmaceutical and biological applications.**

3 Andrew J. Capel^{1*}, Rowan P. Rimington¹, Mark P. Lewis¹ and Steven D. R. Christie^{2*}

4

5 ¹ School of Sport, Exercise and Health Sciences,

6 Loughborough University,

7 Loughborough,

8 United Kingdom.

9

10 ² School of Science,

11 Loughborough University,

12 Loughborough,

13 United Kingdom.

14

15 *** Corresponding Authors:**

16 Dr. Andrew J. Capel

17 a.j.capel@lboro.ac.uk

18 Dr. Steven D. R. Christie

19 s.d.christie@lboro.ac.uk

20 **1. Abstract**

21 3D printing is becoming increasingly prevalent in modern chemistry laboratories. The ability to design,
22 prototype and print functional parts for specific reactions, to embed catalytic or analytical functionality into
23 a chemical device, or even to print common laboratory hardware and teaching aids is a useful addition to
24 the chemists' array of tools. Although 3D printing is becoming more mainstream in general, and access to
25 affordable desktop printers has increased significantly, there are some design principles and materials
26 considerations that need to be considered before employing 3D printed devices in the chemistry laboratory.
27 There is also a learning curve to using computer aided design (CAD) and printing software which must be
28 overcome, and there are still some barriers to entry with respect to specialist hardware associated with more
29 high-end instrumentation. Nonetheless, the recent progress that has been made in this field is encouraging,
30 with these printing technologies offering many advantages over traditional methods. This review sets out
31 to highlight some of the significant advances that have been made in this growing area within the last
32 decade.

33 **2. Introduction**

34 The advent of 3D printing, or additive manufacturing (AM), has seen recent advances in many areas of
35 science and engineering. With respect to chemistry, and where chemistry overlaps with materials and
36 biology, this has happened most notably since around 2012. The ability to print chemical reactors provides
37 opportunities for the chemist to think differently about their design: to introduce non-traditional geometries;
38 to include embedded sensor technologies; to quickly iterate designs to optimise reactions; and even to
39 prepare relatively simple parts that can be utilised as teaching aids. However, this needs to be tempered
40 against the requirement for containment of the chemistry itself: there are limitations on the solvent
41 compatibility with the various materials that can be printed. In addition, print resolution and the design
42 itself needs to be considered to achieve a successful design. Nonetheless, AM does offer a potential step-
43 change in how chemistry is approached, and with the cost of printers decreasing and the number of available
44 materials increasing, it is set to become even more useful. AM refers to a subset of processes which fabricate
45 parts by converting a computer aided design (CAD), via a digital STL (standard tessellation language) file,
46 into a physical product. These technologies can be divided into 7 subsections, providing a detailed structure
47 to categorise current and future printing processes. These subsections include binder jetting, directed energy
48 deposition, material extrusion, material jetting, powder bed fusion, sheet lamination and vat
49 photopolymerisation.¹ Whilst each process is unique in the method and material of manufacture, each
50 technique is based upon a sequential layer-by-layer deposition of print material. A more detailed description
51 of these print processes is summarised below (Table 1) as well as in several recent reviews.²⁻⁵ Ultimately,
52 considerations including required print resolution, speed, cost and material determine the selection of the

53 appropriate printing process for the desired chemistry application. This review aims to outline the diverse
54 scope of research undertaken with respect to the application of 3D printing within the field of chemistry, as
55 well as highlighting future research directions and the challenges that need to be overcome. Specifically,
56 this review will emphasise the application of 3D printing for the generation of everyday laboratory hardware
57 and bespoke analytic instrumentation, as well as the development of teaching aids to illustrate concepts in
58 formal teaching environments. Also highlighted will be the manufacture of custom micro- and millifluidics
59 featuring integrated fittings, valves and pumps as well as embedded analytical functionality. The
60 development of catalytically active surfaces that promote chemical conversions and accelerate reaction
61 progress will be discussed. The construction of biological perfusion devices or bioreactors which optimise
62 chemical conversions based on biological responses will also be covered. Finally, the review will cover the
63 fabrication of point of care and personalised medication designed to meet the specific demands of the
64 patient.

Table 1: A summary of additive manufacturing technologies, exemplar processes and commonly used print materials. Abbreviations: three-dimensional printing (3DP), binder jetting (BJG), laser engineered net shaping (LENS), directed light fabrication (DLF), direct metal deposition (DMD), fused deposition modelling (FDM), robocasting/direct ink writing (DIW), multi-jet modelling (MJM), polyjet modelling (PJM), continuous inkjet printing (CIJ), drop-on-demand (DoD), laser sintering (LS), direct metal laser sintering (DMLS), selective laser melting (SLM), electron beam melting (EBM), selective heat sintering (SHS), laminated object manufacturing (LOM), ultrasonic additive manufacture (UAM), stereolithography (SL), digital light processing (DLP), continuous liquid interface production (CLIP), two-photon polymerisation (2PP), polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polystyrene (PS), polyvinyl alcohol (PVA), polyethylene terephthalate (PET), polyethylene terephthalate glycol (PETG), polypropylene (PP), polyether ether ketone (PEEK).

Process Category	Process Definition	Exemplar Processes	Common Materials
Binder Jetting	A liquid bonding agent is selectively deposited to join powder materials	3DP, BJG	Metals composites including Al, Cu, Fe, Ni and Co based alloys as well as silica, glass and graphite-based ceramics.
Directed Energy Deposition	Focused thermal energy is used to fuse materials by melting as they are being deposited	LENS, DLF, DMD	Metal powders including stainless steels, nickel-based alloys e.g. Inconel, aluminium, titanium, cobalt and copper.
Material Extrusion	Material is selectively dispensed through a nozzle or orifice	FDM, DIW	Thermoplastic polymers including PLA, ABS, PC, PS, PVA, PET, PETG, PP as well as composite materials such as glass and carbon reinforced composites.
Material Jetting	Droplets of build material are selectively deposited.	MJM, PJM, CIJ, DoD	UV curable photopolymers typically acrylates, epoxides or urethanes.

Powder Bed Fusion	Thermal energy selectively fuses regions of a powder bed.	LS, DMLS, SLM, EBM, SHS	Metal alloys including stainless steels, nickel-based alloys e.g. Inconel, aluminium, titanium, cobalt and copper. Polymers such as NYLON-12, PP, PEEK and some experimental ceramics and reinforced composites
Sheet Lamination	Sheets of material are bonded to form an object	LOM, UAM	Sheets of paper, thermoplastics such as PVC or softer metals such as aluminium or copper.
Vat Photopolymerisation	Liquid photopolymer in a vat is selectively cured by light-activated polymerization	SL, DLP, CLIP, 2PP	UV curable photopolymers typically acrylates, epoxides or urethanes.

3. Laboratory Equipment

Recent reductions in the cost of 3D printing equipment has increased the affordability and accessibility of these technologies within research and teaching laboratories. This has driven an increase in the use of 3D printing for repairing, customising or developing bespoke laboratory equipment at a fraction of the cost of commercial alternatives. Many of these designs are being made open source within online repositories such as Thingiverse, the National Institutes of Health (NIH) 3D Print Exchange, and indeed for printers themselves via the RepRap project (see further information) or as part of peer reviewed academic journals. This cross-fertilisation of intellectual property has allowed designs to be shared throughout the community and iteratively developed to identify and correct design flaws. Consequently, there is now a multitude of general laboratory and analytical hardware freely available to download and print for use in chemical and biochemical laboratories.

3.1 General Laboratory Hardware

A diverse range of general laboratory hardware has been produced and or adapted via the use of 3D printing. Indeed many CAD designs, often in the form of .STL files, for a myriad of both simplistic and more complex laboratory hardware have been made open source and freely available to download online for example on websites such as Thingiverse. Once purchased, everyday hardware items need regular replacement due to breakages, with custom parts regularly commissioned to meet the requirements of experimental demands. This strategy has been exemplified by Joshua Pearce, who has extensively used fused deposition modelling (FDM) to manufacture a range of commonplace laboratory items including a sample rotator, mixer and shaker,⁶ a nutating mixer,⁷ and a syringe pump.⁸ Other examples of printed pumping systems include miniature peristaltic pumps via the manufacture of a housing that encases the pump motors.⁹ Further developments in this area have produced the first 3D printed microfluidic pump that is null in its electrical requirements. The device, powered by the human finger, uses two fluidic diodes that act as one-way valves restricting fluid flow from left-to-right. The finger-actuated membrane creates an air pressure that actuates the corrugated membrane within a fluidic reservoir, facilitating flow via opening of the right and closing of the left diode. Removal of this pressure reverses the diodes responses and re-fills the fluid reservoir. Repetition of this process creates a continuous unidirectional microfluidic flow capable of achieving rates of 157 μL per minute.¹⁰

Solvent compatibility and permeability data for a multitude of common printing materials including polypropylene (PP), polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), and polyethylene terephthalate glycol (PETG) have also been screened for the development of custom laboratory hardware including beakers, Erlenmeyer and round bottom flasks, test tubes, custom tube racks and funnels. Part

functionality was demonstrated via a palladium catalysed cross coupling and nickel catalysed hydrothiolation conversion.¹¹ Custom multi-well culture plates have also been manufactured via laser sintering (LS) from polyamide-12, allowing sterilisation and reuse.¹² Finally, sample preparation and extraction, two of the most widely used laboratory techniques, are also being transformed. Small molecule extraction has been demonstrated utilising a rubber composite to fabricate custom sorbents which integrate with standard Eppendorf tubes. These porous FDM sorbents were demonstrated through the successful extraction of glimepiride from water.¹³

3.2 Analytical Hardware

Development of specialist analytical instrumentation requires the design of complex custom parts. Utilisation of 3D printing to prototype and manufacture bespoke devices is therefore desirable to reduce associated production times and costs. This principle has been notably documented by Brett Paull. Temperature and pressure stable high-performance liquid chromatography (HPLC) columns have been manufactured using selective laser melting from Ti-6Al-4V titanium alloy. The column designs featured two-dimensional (2D) and 3D serpentine, as well as 3D helical channel geometries. The channels were internally functionalised post-print with a poly(butyl methacrylate-co-ethyleneglycoldimethacrylate) stationary phase. The functionality of the designs was demonstrated through the separation of proteins from complex mixtures.¹⁴ The same group has also utilised FDM to print a single piece photometric detector body with slit, which when integrated with a commercial light-emitting diode (LED) and photodiode either side of capillary tubing, allowed quantitative photometric detection.¹⁵ Finally, inkjet printing has been applied to the production of a chemiluminescence detector used in the detection of hydrogen peroxide in urinary and coffee extracts,¹⁶ as well as the manufacture of polymer thin layer chromatography (TLC) platforms, demonstrated by the planar separation of both visible dyes and fluorescently tagged proteins.¹⁷ Other demonstrations of planar chromatography have seen customisation of an extrusion printer with a silica slurry doser utilised to manufacture TLC plates, demonstrated by separation of a commercially available dye mixture.¹⁸ Hollow nuclear magnetic resonance (NMR) spectroscopy tube/spinner combinations out of NMR-transparent polyamide have also been printed using FDM. The entire build was carried out within an atmosphere-controlled glove box, with the build being paused allowing the reactants for a Sonogashira coupling to be encapsulated within. Inside this gas tight and pressure resistant reaction vessel a series of aryl naphthylalkynes were synthesised, with the reaction progress being monitored via NMR spectroscopy.¹⁹ Other demonstrations of printed analytical hardware have included ultraviolet-visible (UV-Vis) spectroscopy,²⁰ light emitting diode array detection,²¹ flow cytometry,²² magnetic resonance imaging,²³ scanning electron microscopy,²⁴ polymerase chain reaction,²⁵ low temperature plasma ionization,²⁶ electrophoresis,²⁷ and direct spray ionization mass spectrometry.²⁸

Insert Figure 1

4. Teaching Aids

Perhaps one of the easiest entries into 3D printing is through the production of teaching aids. These can range from laboratory items used in undergraduate teaching, through to classroom items that help to illustrate concepts in formal teaching environments. With increasing access to open-source libraries of printable educational material and affordable printing technology, and given the economic constraints governing all teaching environments, these technologies have the potential to substantially reduce teaching costs whilst stimulating the development of innovative new teaching methodologies. An area garnering considerable interest is the manufacture of 3D model kits which conceptualise complex scientific phenomena in a more educationally stimulating format. These model kits have been extensively utilised to visualise molecular structures, orbitals and symmetry^{29–36} Commercially, the cost of these model sets used in a large classroom setting can often be prohibitive, whereas when printed each individual item can be produced for a fraction of the price if access to a desktop printer is provided. Extension of this concept to other types of teaching aids has seen the production of reaction progress surfaces to represent spectroscopic data in a more engaging format,³⁷ as well as energy profiles to visualise local and global minima in a simplistic manner.³⁸ Experimental teaching aids have also been conceptualised, introducing students to the basics of continuous flow through simplistic mixing devices that illustrate the principles of flow chemistry and mixing.³⁹ Workshops instructing the building and use of REPRAP 3D printers for classroom settings have also been undertaken. Teachers were able to assemble and use 3D printing instrumentation, describing a transformative and empowering effect of this technology within the classroom environment.⁴⁰

Insert Figure 2

5. Chemical Fluidics

The utilisation of 3D printing to manufacture fluidic devices for the preparation, synthesis and analysis of small volumes of chemical reagents is becoming increasingly prevalent within academic environments.⁴¹ These devices, generically referred to as chemical reactors, or more specifically micro- or millifluidics, lab-on-a-chip (LOC) or miniaturised total analysis systems (μ TAS), are more traditionally manufactured via processes including chemical etching, injection moulding, photolithography, soft lithography, micro-machining, hot embossing, thermoforming and laser ablation.⁴² Many of these processes fabricate a template or master, typically using polydimethylsiloxane (PDMS) as the moulding material. PDMS has many desirable properties such as its low material cost, simplistic integration with tubing and fittings, transparency, gas permeability and biocompatibility making it desirable as a material for fluidic applications. However, it is prone to chemical swelling in many organic solvents, deforms at relatively low pressures ($>1 \times 10^5$ pascals) and is known to absorb hydrophobic drug compounds. Furthermore, these approaches necessitate a final step whereby the master must be chemically bonded to another surface to create the final piece, often causing issues with misalignment and poor interlaminar adhesion.⁴³ Whilst each of these processes are capable of manufacturing fluidic devices featuring intricate mixing pathways and embedded analytical functionality, accessible geometries are mostly restricted to 2D planar channel networks. Many of these techniques tend to be time consuming and complex, requiring specialist equipment/training as well as expensive clean room facilities. Consequently, manufacturing costs escalate with increasing design complexity, making iterative designs financially wasteful and part production times lengthy.⁴⁴ However, the recent technological advancements associated with high resolution and cost-effective 3D printing has facilitated the uptake in printed micro- and milliscale fluidics. 3D printing, whilst currently not capable of matching the manufacturing resolution of gold standard processes such as photolithography, does promote an iterative design process, whilst often simplifying the manufacturing process into a single step. The comparatively high design freedom of 3D printing also allows more complex geometries to be realised, often within a few hours of conceptualisation. This approach has made fluidic design and manufacture more accessible to a broader audience, and consequently is driving substantial innovation in the research area.⁴⁵

5.1 Micro- and Milli-fluidics

Some of the first articles on the use of 3D printing in chemistry appeared around 2012. Leroy Cronin was amongst the first to recognise the potential for additive manufacturing in preparative chemistry. Cronin published his “reactionware” which used FDM techniques to provide devices capable of performing synthetic chemistry.^{46,47} Of note, even these early devices showed how advanced techniques could be easily

implanted into the devices: they contained optical viewing ports, could be monitored by UV-Vis spectroscopy and even utilised electrochemical components. This reactionware approach has grown to incorporate multi-step reactions including purification regimes,⁴⁸ and more recently has focussed on the production of valuable pharmaceutical compounds such as ibuprofen.^{49,50} These latter exemplar studies are multi-step, multi-solvent processes that incorporate valves to move the chemistry between the different stages. The authors suggest that the use of this open-source approach to chemistry will promote the sharing of chemistry know-how, whereby the digital blueprints for a device can be downloaded and printed, allowing a simplistic set of instructions to be followed to produce the chemical of choice. The possibility of using such devices to enable production of drugs in, for example, disaster zones remains to be seen. However, the ability to share the digital file for the reactionware itself does allow for the distribution of knowledge on a hitherto unseen scale.

Related advances in flow chemistry have also been achieved. Again, Cronin has been among the primary advocates. These relatively simple early devices demonstrated the potential to integrate printed fluidic devices with accessible analytical instrumentation such as inline UV-Vis, electrospray ionization mass spectrometry (ESI-MS) and attenuated total reflectance infrared (ATR-IR) spectrophotometers to rapidly produce experimental data.⁵¹⁻⁵³ The simplicity of the devices does, however, belie the technical aspects of the printing needed to be calculated to achieve a working device. The need to understand the material properties, printing parameters, chemical compatibilities etc. cannot be overestimated. However, this and other pioneering papers have now described most of the underpinning factors for other people to use. Capel et al described most of the fabrication techniques in an early 2013 paper, and also went on to describe how the design elements are critical to the success of any printed device.⁵⁴ Indeed, Breadmore has shown how the intricacies of printing geometry can affect the mixing regime within a fluidic device.⁵⁵ FDM type printing will produce striations in the device itself due to the nature of the process; by altering the direction of the print relative to the flow of the chemical reaction, natural variations in the wall topography can be used to produce a mixing effect. This is perhaps a relatively obvious observation, but the utilisation of this to cause a desired effect is an additional benefit of the technology. Breadmore has also compared different printing techniques and assessed their utility for flow devices.⁵⁶ The advances in the additive manufacturing technology now allow a print resolution of the order of a few hundred microns utilising standard printing equipment, which brings the processes into the scale of conventional microfluidic devices.⁵⁷ One of the main advantages of 3D printing over these more conventional techniques is the speed of printing: either to produce multiples of the same design, or variants where an improvement through design iteration can be achieved.⁵⁸ Hilton and co-workers have prepared and used inexpensive polypropylene reactors that utilise existing reactor technologies, in terms of pumps etc. for S_NAr reactions.⁵⁹ Sans and co-workers have demonstrated that other reactor designs are just as amenable to 3D printing.⁶⁰ The design and printing of

miniaturised continuous flow oscillatory baffled reactors (mCOBR) using a relatively inexpensive printer has been shown to produce monodisperse silver nanoparticles, with better particle size distribution than more conventional tubular reactors. In perhaps one of the most advanced designs to date, Kappe and co-workers have produced a printed stainless steel reactor for continuous difluoromethylations.⁶¹ Computational fluid dynamic modelling produced a flow channel design that was printed. Of note, the design incorporates a quench channel and a cooling channel, both of which are included in the design and print. In addition, the manufacture also anticipates the removal of residual metal powder from the printing process, and small holes are designed to facilitate removal, which are then sealed post manufacture.

Insert Figure 3

5.2 Templates, Moulds and Masters

Utilisation of 3D printing to generate a template, master or mould for the fabrication of a PDMS fluidic device provides many of the advantageous features of 3D printing, allowing iterative designs to be rapidly and inexpensively screened, whilst still retaining many of the desirable properties of PDMS. Each design iteration can be produced on demand for a very low cost, without the requirement for clean room facilities or manufacturing expertise. This approach has been most succinctly investigated by Daniel Filipini, who has utilised stereolithography (SL) to rapidly fabricate soft lithographic masters for a diverse range of affordable PDMS microfluidic devices. The flexibility of this technique has been demonstrated through the production of 2D and pseudo-3D fluidic devices, featuring microscale channel geometries, and intricate features such as micromixers, unidirectional check valves and multifluidic levels. Whilst the process developed did reduce the number of manufacturing steps required to produce a LOC device, the proprietary acrylate-based print resin utilised to manufacture the masters did prevent complete PDMS curing, necessitating the addition of an airbrushed biocompatible ink coating onto the surface of the master.^{62,63} An alternative post-processing methodology has subsequently been proposed, whereby the addition of a post print oven cure, oxygen plasma treatment and surface fluorination remove the necessity for an ink coating. By employing this approach, the group were able to produce intricate channel geometries including a “basket-weaving” network and a chaotic advection mixer, as well as demonstrating functional peristaltic valves.⁶⁴ These post processing steps have subsequently been removed entirely by utilising inkjet printing and a UV photoresin to produce PDMS fluidics for cell-based assays.⁶⁵ Other novel approaches have seen water soluble sugar and polyvinyl alcohol (PVA) masters printed via FDM, allowing the scaffold to be easily dissolved away following immersion in PDMS and resin curing.^{66,67} Finally, sacrificial ABS scaffolds have been printed using FDM, whereby subsequent removal of this scaffold is readily achieved by dissolution of the polymer in acetone. Utilisation of this method allowed external equipment such as heating

elements or electronic components to be simplistically embedded into the fluidic device, as well as the generation of intricate 3D channel geometries.⁶⁸

5.3 Integrated fittings, valves and pumps

Achieving high throughput experimental data and accurate liquid handling requires integration of the fluidic device with pumps, valves and fittings capable of manipulating flow with precision. These features can be integrated utilising equipment external to the device or by miniaturisation and integration within the device. Each of these integrated features have been demonstrated by Gregory Nordin and Adam Woolley. This group has utilised high resolution digital light processing stereolithography (DLP-SL) to demonstrate the fabrication of printed microfluidic membrane valves. Combining two of these microfluidic valves with a displacement chamber allowed the realisation of a compact pump capable of flow rates as high as 50 $\mu\text{L}/\text{min}$. Furthermore, by combining five valves with a displacement chamber, a methodology to create a simplistic 3-to-2 multiplexer with an integrated pump was demonstrated. In addition to serial multiplexing, these devices were also shown to have functionality as microfluidic mixers.⁶⁹ Another notable example has seen the fabrication of a motor driven miniaturised peristaltic pump, using a gear based system to invoke peristalsis. The pump was reproducible across an impressive flow range between 40 and 230mL/min, whilst operating at back pressures as high as 25 kPa.⁷⁰ Integrated valves can be utilised in isolation or in tandem to switch or redistribute fluid flow within a flow device. This premise has been exploited utilising SL to manufacture a four-valve fluid switch connected to a downstream cell culture chamber, employing an electronically actuated 100 μm thick non-elastomeric printed membrane to control fluid flow throughout the part.⁷¹ Another demonstration of fluidic valves has seen multi-material 3D printing exploited, allowing the fabrication of flexible membranes which exploit variabilities in material stiffness to enable valve actuation, allowing multiple independently actuated valves to be located within close proximity to one another.⁷² Integration of fluidic devices to external instrumentation, such as pumps, is typically achieved by interfacing through connectors/fittings, with the most commonly used of these being Luer lock, hosed or threaded in design. Several research groups have successfully integrated these fittings into printed fluidic devices. This principle has been exploited utilising SL to manufacture low pressure female Luer connectors allowing tubing to be reversibly interfaced through commercially available barbed adapters.⁷³

Insert Figure 4

5.4 Embedded Technology

Much of the work in 3D printed reactor technology thus far has focussed on the printing of reactor vessels, whether these are of batch or flow type devices. However, the nature of 3D printing also offers the potential

to install other features to increase the utility of the reactor. Monaghan et al demonstrated that fibre optics can be embedded into 3D printed structures and still retain their functionality.⁷⁴ Following on from this, the same group were able to place fibre optics within fluidic devices prepared via SL printing.⁷⁵ There is a depth of work here, for example, as to the design and implementation of the fibres, the calibration of the device and alignment of the fibres, and the light source/detector. Using the fibres as conduits for UV-Vis spectroscopy, it was then possible to follow a reaction by spectroscopic means. In separate work, different designs were prepared that utilised existing lab equipment to achieve on-line reaction monitoring.⁷⁶ Here, a device was prepared that could be inserted in the flow cell of the diode array detector of a HPLC. By measuring an existing piece of equipment, a CAD file was generated to produce the requisite fluidic device. Once printed, this was fitted with optical windows and used directly in the HPLC optical detector to monitor the reaction. Further, the optimisation of the reaction under study was automated by a SIMPLEX algorithm using temperature and flow rate as variables. A secondary flow device was also prepared that was designed to fit within the heated column compartment of the HPLC. Embedded fibre optics have also been employed in the direct detection of microparticle detection and counting.⁷⁷ Particle synthesis in microfluidic devices can be achieved in commercial chips, however the analysis of the particles generally takes place in a secondary process. By designing an auxiliary flow device with embedded fibres optics, Hampson et al were able to detect and size particles by measuring the light intensity as the particles occluded the light source. Notably, the reproducibility of the analysis was optimised via a genetic algorithm. Embedded graphite and silver electrodes incorporated via a commercially available 1/4-28 threaded fitting, allowing electrochemiluminescence generated at the electrodes to be measured inline via an inline CCD camera, have also been realised via SL printing.⁷⁸ Ambrosi and Pumera have reported on the preparation of bespoke electrodes via a metal printing process.⁷⁹ These uniquely shaped electrodes can then be tailored for different applications, such as capacitors and pH sensors. 3D printed flow plates have been incorporated into an electrochemical cell for the electrolysis of water.⁸⁰ Construction of the plates was achieved by printing in polypropylene, followed by administering a layer of silver and construction of the cell itself.

Insert Figure 5

6. Catalysis

3D printing of catalytically active functionalised parts can provide bespoke surfaces that promote chemical conversions. This functionalisation can be achieved via modification of the chemical composition of the print material either prior to or following the print process, or by printing the part from a material with inherent catalytic properties. Utilising the design freedom associated with 3D printing, allows complex structures with high surface areas to be realised, theoretically increasing the rate at which the catalyst acts. This form of catalyst immobilisation allows increased catalyst recovery, as well as increasing catalytic activity as a consequence of the solid support providing chemical, thermal, and mechanical stabilisation to the catalytic species.

Each of these approaches has been successfully demonstrated utilising a custom extrusion-based deposition apparatus. Colloidal Al_2O_3 ceramic ink has been printed into a highly porous cylindrical lattice, followed by a post-process calcination at 1500°C . These lattice structures acted as Lewis acids in the Biginelli and Hantzsch synthesis of pharmacologically active dihydropyridines and dihydropyrimidinones. The scaffolds could be recovered for subsequent re-use without any decrease in catalytic activity.⁸¹ The same group also utilised this methodology to generate a $\text{Cu}/\text{Al}_2\text{O}_3$ scaffold and demonstrated functionality through a range of copper catalysed Ullmann reactions.⁸² Finally, a complex multi-material catalytic scaffold was produced, whereby a SiO_2 monolithic support was selectively coated with both copper and palladium functionality and utilised to perform heterogeneous multicatalytic multicomponent reactions allowing the synthesis of a multitude of substituted 1,2,3-triazoles.⁸³ Other research has seen FDM used in combination with custom TiO_2 infused ABS nanocomposites to photocatalyze the degradation of fluorescent rhodamine 6G in solution.⁸⁴

Electron beam melting of titanium (Ti6Al4V), cobalt chrome (CoCr) and stainless steel (316L), followed by metal cold spraying or electrodeposition of nickel(0) and platinum(0) has been used to develop catalytic static mixers. These static mixers were evaluated across a broad range of continuous flow hydrogenations, generating a series of compounds with alkene and carbonyl functionality. Utilising metal powder sintering/melting printing processes allow thermally and chemically stable parts to be generated, which are suitable for synthesis at elevated pressures, making these high-end parts suitable for use across a wide range of chemical applications.⁸⁵ Direct write printing has also been demonstrated as a suitable manufacturing method for the production of stainless steel scaffolds (316L), with post process deposition of an aluminosilicate (ZSM-5) to functionally coat the scaffold. This scaffold was utilised for the subsequent catalytic conversion of methanol to dimethylether and to olefins.⁸⁶

DLP-SL has also been utilised for the preparation of monolithic catalysts. Negative moulds generated via this process were packed with α -Al₂O₃ powder and sodium silicate. The dried material was then heated at 850°C for 8 hours to burn off the printed case and reveal the monolithic structure. These structures were impregnated with Mn- and Na₂WO₄ containing catalytic compounds and used to accelerate the production of methane in the oxidative coupling of methane.⁸⁷ Catalytically active cuvette adapters and milli-fluidics were also printed utilising SL, producing architectures by photopolymerizing bifunctional molecules. These printed architectures were functionalised with carboxylic acid, amine, and copper carboxylate functionalities, and demonstrated across Mannich, aldol, and Huisgen cycloaddition reactions. Reactions were undertaken in both static and flow environments, with *in situ* kinetics used to determine reaction progression.⁸⁸

Insert Figure 6

7. Biotechnology

The synergy of devices that optimise chemical reactions, with those in which the biological responses to such compounds are observed, is a natural evolution. As such, 3D printing technologies have also seen increased recent uptake in the fields of bioanalytical systems, as well as biomedical engineering and bioprinting.^{89,90} The increasing prevalence of these printed systems has been a result of the spiralling costs associated with drug development and pharmaceutical screening. Today, each new clinically approved pharmaceutical compound takes more than 10 years and \$2.5 billion to be brought to market.⁹¹ The requirement for the development of more predictive biological models that represent the *in vivo* niche is necessitated by this requirement to accurately predict drug efficacy, with big pharmaceutical companies now subscribing to this “fail early and fail cheaply” mandate.⁹² This approach has been adopted to not only rapidly remove drugs with low efficacy or high toxicity, but to prevent potentially active compounds from being mistakenly removed from testing due to the poor predictive nature of the model. The use of advanced 3D printing techniques to create devices capable of influencing pharmaceutical testing is in response to the complex multi-step processes of traditional microfluidics. The efficacy of 3D printing in bio-microfluidics has previously been discussed extensively.⁹³ Here, the use of one-step user friendly production methods allows researchers generating such technologies to rapidly iterate designs based on biological feedback, in response to various engineering alterations. It is hoped that this will aid the translation of these devices toward consumer facing environments, primarily due to the rapid prototyping nature of 3D printing decreasing the time to design and manufacture physiologically relevant systems. Critically, the biological functionality of prototypes also enables the production of a powerful intermediate technology capable of producing crucial proof of concept, optimisation and influential academic data. Care must be taken, however, to assess the biocompatibility of any print material for use within the biological system under study. Many of these 3D printed parts are often taking the place of standard glass or plasticware that is readily available and where biocompatibility has been known for many years. When printing with different polymeric materials, the scientist must be cognisant of not only the compatibility of the polymer, but also of leaching of any additives or monomeric materials that could have a diverse effect on the biological system. Thorough testing of the system will be required in each case. A myriad of static 3D printed devices have been produced that incorporate biological functionality.^{94,95} However, the degree of physiological biomimicry of samples often remains limited. For biological devices to be added as modules onto the backend of chemical reactors, a system that incorporates perfusion is required. In this regard, this review will highlight those systems that are 3D printed, enable perfusion and incorporate mammalian cellular biological samples.

7.1 Biological Perfusion Reactors

3D printed devices that incorporate cellular samples within a perfused environment is a relatively new, yet rapidly developing, research area. Work from the laboratory of Dana Spence produced the first 3D printed biofluidic device.⁹⁶ This system contained eight channels, each receptive to commercially available porous membranes for cell culture that facilitate drug diffusion toward the sample of interest. This was confirmed via examination of the membrane integrity of endothelial cells in response to perfused compounds. Further contributions of Spence's laboratory toward this area have focussed on the analytical capability and biology within systems, evidenced by the integration of reusable electrodes and drug metabolism in 3D culture environments of multicellular tumour spheroids within fluidic devices.^{97,98} Pertinently, the developments of these 3D printed systems have enabled the pharmacokinetic profiling of candidate molecules,⁹⁹ whilst also generating novel physiological data surrounding pathological conditions.¹⁰⁰ Other 3D printed bioanalytic devices have also been reported, such as miniaturised adenosine triphosphate (ATP) bioluminescence sensing,¹⁰¹ clinically relevant whole organ biomarker profiling,¹⁰² and electrochemical influenza virus detection.¹⁰³ Such technological developments hold significant promise within the drug discovery process. There remains however, a distinct requirement for devices that are 3D printed, analytical, and encompass physiologically representative engineered tissue in 3D; various groups have endeavoured to address this need. Macrofluidic bio-perfusion systems 3D printed using dual extrusion FDM have been developed for the cultivation of human osteoblasts within calcium phosphate surface coated mesh scaffolds.¹⁰⁴ Whereas other strategies have focussed on the inclusion of 3D cell cultures within microfluidics,¹⁰⁵ here 3D spheroid cultures of the immortalised liver cell line (HepG2) in devices 3D printed using SL would be of specific interest.¹⁰⁶ Toh and colleagues noted preferential printing of microfluidic device features in SL compared to polyjet modelling (PJM), in addition to improvements in the 1A1 and 3A4 cytochrome P450 enzyme isoforms when liver cells were cultured in the perfused 3D environment. This is specifically relevant due to the integral role of these enzymes in drug metabolism.

Further work in this area has focussed on the production of microfluidic devices that are derived using bespoke photo-polymer resin formulations. These formulations were shown to be biocompatible using Chinese hamster ovary (CHO) cells and primary mouse hippocampal neurons.¹⁰⁷ Developments such as this are essential in the translation of chemical reaction technology to biological applications, due to the toxicity of various photo-curable 3D printing polymers. This is further outlined by the prior use of polymer coatings to improve cellular compatibility in devices 3D printed via PJM.¹⁰⁸ The chemical complexity of UV/laser curable resins (favoured for microfluidics) have stimulated lines of research across multiple groups to establish the biocompatibility of such polymers, in addition to the synthesis of custom bio-resin formulations. This data will be of critical importance if the advances in 3D printed flow chemistry are to be realised within cell biology and/or tissue engineering, and ultimately influence pharmaceutical drug development.

Insert Figure 7

8. Drug Delivery

A tailored approach to drug delivery and the manufacture of personalised medicines, with bespoke prescriptions being rapidly generated on demand to meet the specific pharmacogenomic, anatomical and physiological demands of the patient, has been hypothesised through the application of 3D printing technologies.¹⁰⁹ Personalised medicine has the capacity to reduce the incidence of under- and over-dosing of prescription medicines, as well as producing prescriptions at the point of dispensing or point of use.¹¹⁰ Extrapolation of this hypothesis has led to a belief that these technologies can be utilised for the generation of pharmaceuticals on demand in environments whereby drug availability is restricted by location i.e., space expeditions or war zones. There are however a significant number of hurdles which must be overcome to make this belief a reality. To ensure drug uniformity, stability and sterility careful consideration must be given to process regulations, and thus printed in accordance with good manufacturing practice (GMP) as well as a focus on quality control.¹¹¹ Printing of drugs is also currently still considered low-throughput and development of more scalable models is necessary to increase uptake of this technology. As the field develops, it must also prove itself against other, perhaps simpler, solutions, such as adjusting dosage via prescription of standard, or multi-drug pills. Nonetheless, the potential advantages and the interest in the area has seen much activity in recent years.

This research niche is rapidly expanding and as such has been the subject of a number of more comprehensive review articles.^{112,113} To date the most widely utilised printing processes for the manufacture of personalised medicines are inkjet-powder bed (also known as binder jetting or simply 3D printing), FDM and continuous inkjet printing or drop-on-demand (CIJ/DoD).^{114,115} For each of these processes reproducibility and reliability is intrinsically linked to the selection of a suitable “ink” formulation and therefore careful consideration must be given to match the active pharmaceutical ingredient (API) with an appropriate carrier. The inkjet-powder bed process deposits drug loaded liquids onto an excipient powder bed, allowing the generation of highly complex and bespoke immediate, extended and multi-release tablets. Alternatively, binder solutions can also be printed onto drug laden powder beds. In 2015 the US Food and Drug Administration (FDA) approved the use of Spritam®, the first drug manufactured utilising 3D printing technology, for oral administration to treat partial onset seizures in people suffering from epilepsy.¹¹⁶ Application of this technology is however limited by the lack of low-cost commercially available inkjet-powder bed printers.¹¹⁷ With the rapid increase in commercially available low-cost printers, drug printing via FDM is therefore becoming increasingly prevalent as a low-cost alternative. APIs can be loaded into

the filament crudely through immersion of the raw polymer into a drug-laden solution,¹¹⁸ or more subtly via hot-melt extrusion of custom filaments.¹¹⁹ Production of oral drug doses via this methodology is limited, with print formulation and ultimately drug release profiles being restricted by fixed filament composition. This significantly limits the freedom to produce tailored drug dose or drug combinations and moves further away from the personalised medicine paradigm. Demonstrations of this approach have included loading PVA filaments with both 5- and 4-aminosalicylic acid in an ethanolic solution before FDM printing tablets are varying weights and densities.¹²⁰ The same research group has also utilised a hot-melt extruder to generate paracetamol and caffeine loaded filaments, used for the production of oral administration caplets. Finally, more complex compartmentalised multi-drug pills have been realised via FDM, demonstrating that complex medication can be realised utilising these printing technologies.¹²¹ CIJ and DoD are printing process identified as being able to accurately deposit small quantities of drugs onto a substrate suitable for human ingestion. CIJ printing utilises a pressurised flow, generating a continuous stream of charged droplets, which are released through a nozzle. These droplets are then precisely directed onto the substrate by electrostatic plates. DoD printing produces droplets in a more precise manner, generating droplets only when required.¹²² Both processes can accurately deposit APIs solubilised into a solution suitable for printing, and can be precisely dosed dependent on the concentration of the feed solution or the volumes being jetted.¹²³ The flexibility of print formulations has allowed numerous pharmaceuticals to be printed via CIJ/DoD including salbutamol,¹²⁴ riboflavin,¹²⁵ paracetamol,¹²⁶ and caffeine.¹²⁷

Personalised printed medication has the capacity to produce patient specific pharmaceutical formulations with the requisite speed and precision to be considered a viable alternative to the existing drug formulation paradigm. Print formulations can be iterative in nature with feedback from patient response informing future dosing strategies. Open-source expertise shared throughout the medical community, coupled with increasing access to desktop printing equipment, would allow medication to be delivered in point of care and/or remote environments. Whilst increasing print productivity and adherence to regulatory policy are obstacles that need to be addressed, patient specific medication is certainly closer to realisation through the application of these technologies.

Insert Figure 8

Future Directions

This review has set out to illustrate the pace and scale of advances of additive manufacturing as it relates to chemistry and associated fields. The majority of the references contained herein are from the last 5-6 years. This shows how chemists have embraced this relatively new technology and utilised it to advance the chemical sciences. The initial excitement of being able to prepare bespoke tubular reactors has quickly been matched by other innovative approaches in, for example, embedded technologies and reaction monitoring. There are, however, several areas where printing technology needs to advance in order to fully meet the needs of modern chemistry. The primary consideration is materials: the choice of printed reactor is primarily driven by a combination of printing technique and material. Lithography type techniques inevitably use acrylate-based polymers, but this means that there will be a consequence in solvent compatibility. Similarly, if one aims for robust solvent compatibility, the materials choices are more restricted to very inert polymers, or metals. This requires a subset of the available printing techniques; advances in this area of materials choice are critically important to uptake of these technologies. One such advance will likely be the ability to print glass. Glass has been the material of choice for chemists for about two hundred years, due to its transparency, thermal conductivity and relative chemical inertness. Recent advances have shown that printing glass is possible, but the high temperatures required are still a limiting factor.¹²⁸⁻¹³⁰ The resolution of the printing technique can be a limiting factor; in many cases, reactor volumes in the millilitre scale do not require very fine structures, but in order to compete on the truly microfluidic scale, resolution is an issue. This is especially true for removing residual material from within intricate reactor designs. More recently, Rapp has published a hybrid method which produces glass parts.¹²⁹ This process involves dispersing silica nanoparticles in a monomeric matrix. Stereolithography produces the 3D part itself by polymerising the monomer, encompassing the glass particles, and the piece is then sintered to “burn-out” the polymer, and fuse the glass. In this manner, a final glass part is produced. This exciting development thus brings glass into the field of 3D printing. Techniques such as 2 photon polymerisation (2PP) do offer very fine resolution, but again material compatibility becomes an issue. Many of the techniques outlined previously work well for producing discrete parts from a single build process. As illustrated, the ability to create complicated parts with multiple materials, or with embedded functionality is becoming of more interest as chemists look to further probe reactions.^{131,132} This means that chemists are pushing the boundaries of what is possible in additive manufacturing, as illustrated by reaction monitoring using embedded fibre optics. Employing different types of sensors in a single device then becomes a challenge, but the reward is multiple data streams to monitor reactions. The move to online reaction monitoring and reaction optimisation and automation is then an achievable goal. The innovation achieved of chemists and engineers working together is great to see; further advances will no doubt come as the chemist asks about building multi-material devices. The natural advance will then be to have

functional materials embedded within a device e.g., implanting catalysts within the reactor itself. Is it then possible to have multiple catalysts within a single device, or preferable to have multiple devices in series, each with a different catalyst? This will allow multi step synthesis from a single pass of reagents. A modular approach of this type could allow repetitive synthesis of a single molecule, or the preparation of a library of such targets. Similar advances in biology are also taking place. Pharmacists are now looking at completely different methods of drug formulation and tablet preparation. While it may be some time before we see drug synthesis and tablet preparation taking place in a single device, it is not too difficult to see current technologies being put into sequence to achieve that goal. Taken to the next level, chemical and biological reactors can be made available to other groups quite easily by sharing the CAD file. This could be commercial or open source. As illustrated previously, some groups are already sharing designs either in supplementary information, or via websites. All of these advances make 3D printing an attractive option for the chemical sciences in the next decade or so. In many ways, chemists need to “un-think” their own biases about how to conduct reactions in a traditional sense to truly see how the technology can push their science forward. However, the greatest push will come from the lowering in cost of printers themselves. Just a few years ago, printers cost many tens of thousands of pounds, and resided in specialist engineering labs; access was limited, knowledge of CAD and design even more scarce. Now, the price of low-end printers is as low as several hundred pounds for FDM models. Even lithography printers have dropped to a few thousand pounds. This reduction in price is not driven by chemistry, but by loss of patent protection and consumer demand. Nonetheless, the uptake in technology does tend to be faster when people can afford it.

Further Information

Thingiverse can be accessed at <https://www.thingiverse.com/>

National Institutes of Health 3-D Print Exchange can be accessed at <https://3dprint.nih.gov/>

RepRap can be accessed at <https://reprap.org/wiki/RepRap>

References

1. Wong, K. V. & Hernandez, A. A Review of Additive Manufacturing. *ISRN Mech. Eng.* **2012**, 1–10 (2012).
2. Ligon, S. C., Liska, R., Stampfl, J., Gurr, M. & Mülhaupt, R. Polymers for 3D Printing and Customized Additive Manufacturing. *Chem. Rev.* **117**, 10212–10290 (2017).
3. Busachi, A. *et al.* A review of Additive Manufacturing technology and Cost Estimation techniques for the defence sector. *CIRP J. Manuf. Sci. Technol.* **19**, 117–128 (2017).
4. He, Y., Wu, Y., Fu, J., Gao, Q. & Qiu, J. Developments of 3D Printing Microfluidics and Applications in Chemistry and Biology: a Review. *Electroanalysis* **28**, 1658–1678 (2016).
5. Pohanka, M. Three-Dimensional Printing in Analytical Chemistry: Principles and Applications. *Anal. Lett.* **49**, 2865–2882 (2016).
6. Dhankani, K. C. & Pearce, J. M. Open source laboratory sample rotator mixer and shaker. *HardwareX*. **1**, 1–12 (2017).
7. Trivedi, D. K. & Pearce, J. M. Open Source 3-D Printed Nutating Mixer. *Appl. Sci.* **7**, 942 (2017).
8. Wijnen, B., Hunt, E. J., Anzalone, G. C. & Pearce, J. M. Open-Source Syringe Pump Library. *PLoS One* **9**, 1–8 (2014).
9. Balakrishnan, S. *et al.* A Scalable Perfusion Culture System with Miniature Peristaltic Pumps for Live-Cell Imaging Assays with Provision for Microfabricated Scaffolds. *Biores. Open Access* **4**, 343–357 (2015).
10. Sweet, E. C., Mehta, R. R., Lin, R. & Lin, L. Finger-powered, 3D printed microfluidic pumps. *TRANSDUCERS 2017 - 19th Int. Conf. Solid-State Sensors, Actuators Microsystems* 1766–1769 (2017).
11. Gordeev, E. G., Degtyareva, E. S. & Ananikov, V. P. Analysis of 3D printing possibilities for the development of practical applications in synthetic organic chemistry. *Russ. Chem. Bull. Int. Ed.* **65**, 1637–1643 (2016).
12. Lücking, T. H. *et al.* 3D-printed individual labware in biosciences by rapid prototyping: In vitro biocompatibility and applications for eukaryotic cell cultures. *Eng. Life Sci.* **15**, 57–64 (2015).
13. Belka, M., Ulenberg, S. & Bączek, T. Fused Deposition Modeling Enables the Low-Cost Fabrication of Porous, Customized-Shape Sorbents for Small-Molecule Extraction. *Anal. Chem.*

- 89**, 4373–4376 (2017).
14. Gupta, V., Beirne, S., Nesterenko, P. N. & Paull, B. Investigating the Effect of Column Geometry on Separation Efficiency using 3D Printed Liquid Chromatographic Columns Containing Polymer Monolithic Phases. *Anal. Chem.* **90**, 1186–1194 (2018).
 15. Cecil, F. *et al.* 3D printed LED based on-capillary detector housing with integrated slit. *Anal. Chim. Acta* **965**, 131–136 (2017).
 16. Gupta, V., Mahbub, P., Nesterenko, P. N. & Paull, B. A new 3D printed radial flow-cell for chemiluminescence detection: Application in ion chromatographic determination of hydrogen peroxide in urine and coffee extracts. *Anal. Chim. Acta* **1005**, 81–92 (2018).
 17. Macdonald, N. P., Currivan, S. A., Tedone, L. & Paull, B. Direct Production of Microstructured Surfaces for Planar Chromatography Using 3D Printing. *Anal. Chem.* **89**, 2457–2463 (2017).
 18. Fichou, D. & Morlock, G. E. Open-Source-Based 3D Printing of Thin Silica Gel Layers in Planar Chromatography. *Anal. Chem.* **89**, 2116–2122 (2017).
 19. Lederle, F., Meyer, F., Kaldun, C., Namyslo, J. C. & Hübner, E. G. Sonogashira coupling in 3D-printed NMR cuvettes: synthesis and properties of aryl-naphthylalkynes. *New J. Chem.* **41**, 1925–1932 (2017).
 20. Whitehead, H. D., Waldman, J. V., Wirth, D. M. & LeBlanc, G. 3D Printed UV-Visible Cuvette Adapter for Low-Cost and Versatile Spectroscopic Experiments. *ACS Omega* **2**, 6118–6122 (2017).
 21. Prikryl, J. & Foret, F. Fluorescence detector for capillary separations fabricated by 3D printing. *Anal. Chem.* **86**, 11951–11956 (2014).
 22. Bayram, A. *et al.* Integration of glass micropipettes with a 3D printed aligner for microfluidic flow cytometer. *Sensors Actuators, A Phys.* **269**, 382–387 (2018).
 23. Herrmann, K. H., Gärtner, C., Güllmar, D., Krämer, M. & Reichenbach, J. R. 3D printing of MRI compatible components: Why every MRI research group should have a low-budget 3D printer. *Med. Eng. Phys.* **36**, 1373–1380 (2014).
 24. Meloni, G. N. & Bertotti, M. 3D printing scanning electron microscopy sample holders: A quick and cost effective alternative for custom holder fabrication. *PLoS One* **12**, 1–12 (2017).
 25. Mulberry, G., White, K. A., Vaidya, M., Sugaya, K. & Kim, B. N. 3D printing and milling a real-

- time PCR device for infectious disease diagnostics. *PLoS One* **12**, 1–18 (2017).
26. Martínez-Jarquín, S., Moreno-Pedraza, A., Guillén-Alonso, H. & Winkler, R. Template for 3D Printing a Low-Temperature Plasma Probe. *Anal. Chem.* **88**, 6976–6980 (2016).
 27. Anciaux, S. K., Geiger, M. & Bowser, M. T. 3D Printed Micro Free-Flow Electrophoresis Device. *Anal. Chem.* **88**, 7675–7682 (2016).
 28. Duarte, L. C. *et al.* 3D printing of microfluidic devices for paper-assisted direct spray ionization mass spectrometry. *Anal. Methods* **8**, 496–503 (2016).
 29. Scalfani, V. F. & Vaid, T. P. 3D printed molecules and extended solid models for teaching symmetry and point groups. *J. Chem. Educ.* **91**, 1174–1180 (2014).
 30. Penny, M. R. *et al.* Three-Dimensional Printing of a Scalable Molecular Model and Orbital Kit for Organic Chemistry Teaching and Learning. *J. Chem. Educ.* **94**, 1265–1271 (2017).
 31. Jones, O. A. H. & Spencer, M. J. S. A Simplified Method for the 3D Printing of Molecular Models for Chemical Education. *J. Chem. Educ.* **95**, 88–96 (2018).
 32. Rossi, S., Benaglia, M., Brenna, D., Porta, R. & Orlandi, M. Three Dimensional (3D) Printing: A Straightforward, User-Friendly Protocol To Convert Virtual Chemical Models to Real-Life Objects. *J. Chem. Educ.* **92**, 1398–1401 (2015).
 33. Stone-Sundberg, J., Kaminsky, W., Snyder, T. & Moeck, P. 3D printed models of small and large molecules, structures and morphologies of crystals, as well as their anisotropic physical properties. *Cryst. Res. Technol.* **50**, 432–441 (2015).
 34. Wood, P. A. *et al.* The next dimension of structural science communication: simple 3D printing directly from a crystal structure. *CrystEngComm* **19**, 690–698 (2017).
 35. Robertson, M. J. & Jorgensen, W. L. Illustrating Concepts in Physical Organic Chemistry with 3D Printed Orbitals. *J. Chem. Educ.* **92**, 2113–2116 (2015).
 36. Casas, L. & Estop, E. Virtual and Printed 3D Models for Teaching Crystal Symmetry and Point Groups. *J. Chem. Educ.* **92**, 1338–1343 (2015).
 37. Higman, C. S., Situ, H., Blacklin, P. & Hein, J. E. Hands-On Data Analysis: Using 3D Printing to Visualize Reaction Progress Surfaces. *J. Chem. Educ.* **94**, 1367–1371 (2017).
 38. Kaliakin, D. S., Zaari, R. R. & Varganov, S. A. 3D Printed Potential and Free Energy Surfaces for Teaching Fundamental Concepts in Physical Chemistry. *J. Chem. Educ.* **92**, 2106–2112 (2015).

39. Tabassum, T. *et al.* Development and Application of 3D Printed Mesoreactors in Chemical Engineering Education. *J. Chem. Educ.* **95**, 783–790 (2018).
40. Schelly, C., Anzalone, G., Wijnen, B. & Pearce, J. M. Open-source 3-D printing technologies for education: Bringing additive manufacturing to the classroom. *J. Vis. Lang. Comput.* **28**, 226–237 (2015).
41. Dixon, C., Lamanna, J. & Wheeler, A. R. Printed Microfluidics. *Adv. Funct. Mater.* **27**, 1604824 (2017).
42. Faustino, V., Catarino, S. O., Lima, R. & Minas, G. Biomedical microfluidic devices by using low-cost fabrication techniques: A review. *J. Biomech.* **49**, 2280–2292 (2016).
43. Abgrall, P. & Gué, A. M. Lab-on-chip technologies: Making a microfluidic network and coupling it into a complete microsystem - a review. *J. Micromechanics Microengineering* **17**, R15–R49 (2007).
44. Amin, R. *et al.* 3D-printed microfluidic devices. *Biofabrication* **8**, 22001 (2016).
45. Tseng, P., Murray, C., Kim, D. & Di Carlo, D. Research highlights: printing the future of microfabrication. *Lab Chip* **14**, 1491–1495 (2014).
46. Symes, M. D. *et al.* Integrated 3D-printed reactionware for chemical synthesis and analysis. *Nat. Chem.* **4**, 349–354 (2012).
47. Kitson, P. J. *et al.* 3D printing of versatile reactionware for chemical synthesis. *Nat. Protoc.* **11**, 920–936 (2016).
48. Kitson, P. J., Symes, M. D., Dragone, V. & Cronin, L. Combining 3D printing and liquid handling to produce user-friendly reactionware for chemical synthesis and purification. *Chem. Sci.* **4**, 3099–3103 (2013).
49. Kitson, P. J., Glatzel, S. & Cronin, L. The digital code driven autonomous synthesis of ibuprofen automated in a 3D-printer-based robot. *Beilstein J. Org. Chem.* **12**, 2776–2783 (2016).
50. Kitson, P. J. *et al.* Digitization of multistep organic synthesis in reactionware for on-demand pharmaceuticals. *Science (80-.)*. **359**, 314–319 (2018).
51. Kitson, P. J., Rosnes, M. H., Sans, V., Dragone, V. & Cronin, L. Configurable 3D-Printed millifluidic and microfluidic ‘lab on a chip’ reactionware devices. *Lab Chip* **12**, 3199–3522 (2012).

52. Dragone, V., Sans, V., Rosnes, M. H., Kitson, P. J. & Cronin, L. 3D-printed devices for continuous-flow organic chemistry. *Beilstein J. Org. Chem.* **9**, 951–959 (2013).
53. Mathieson, J. S., Rosnes, M. H., Sans, V., Kitson, P. J. & Cronin, L. Continuous parallel ESI-MS analysis of reactions carried out in a bespoke 3D printed device. *Beilstein J. Nanotechnol.* **4**, 285–291 (2013).
54. Capel, A. J. *et al.* Design and additive manufacture for flow chemistry. *Lab Chip* **13**, 4583–90 (2013).
55. Li, F., Macdonald, N. P., Guijt, R. M. & Breadmore, M. C. Using Printing Orientation for Tuning Fluidic Behavior in Microfluidic Chips Made by Fused Deposition Modeling 3D Printing. *Anal. Chem.* **89**, 12805–12811 (2017).
56. Macdonald, N. P. *et al.* Comparing Microfluidic Performance of Three-Dimensional (3D) Printing Platforms. *Anal. Chem.* **89**, 3858–3866 (2017).
57. Walczak, R. & Adamski, K. Inkjet 3D printing of microfluidic structures - on the selection of the printer towards printing your own microfluidic chips. *J. Micromechanics Microengineering* **25**, 85013 (2015).
58. Shallan, A. I., Smejkal, P., Corban, M., Guijt, R. M. & Breadmore, M. C. Cost effective three-dimensional printing of visibly transparent microchips within minutes. *Anal. Chem.* **86**, 3124–3130 (2014).
59. Rao, Z. X. *et al.* 3D-Printed Polypropylene Continuous-Flow Column Reactors: Exploration of Reactor Utility in SNAr Reactions and the Synthesis of Bicyclic and Tetracyclic Heterocycles. *European J. Org. Chem.* **44**, 6499–6504 (2017).
60. Peris, E. *et al.* Tuneable 3D printed enzymatic reactors for continuous-flow biotransformations. *Green Chem.* **19**, 5345–5349 (2017).
61. Gutmann, B. *et al.* Design and 3D printing of a stainless steel reactor for continuous difluoromethylations using fluoroform. *React. Chem. Eng.* **2**, 919–927 (2017).
62. Comina, G., Suska, A. & Filippini, D. PDMS lab-on-a-chip fabrication using 3D printed templates. *Lab Chip* **14**, 424–430 (2014).
63. Comina, G., Suska, A. & Filippini, D. 3D printed unibody lab-on-a-chip: Features survey and check-valves integration. *Micromachines* **6**, 437–451 (2015).

64. Chan, H. N. *et al.* Direct, one-step molding of 3D-printed structures for convenient fabrication of truly 3D PDMS microfluidic chips. *Microfluid. Nanofluidics* **19**, 9–18 (2015).
65. Kamei, K. *et al.* 3D printing of soft lithography mold for rapid production of polydimethylsiloxane-based microfluidic devices for cell stimulation with concentration gradients. *Biomed. Microdevices* **17:36**, (2015).
66. Dahlberg, T. *et al.* 3D printed water-soluble scaffolds for rapid production of PDMS micro-fluidic flow chambers. *Sci. Rep.* **8**, 3372–3382 (2018).
67. He, Y. *et al.* Printing 3D microfluidic chips with a 3D sugar printer. *Microfluid. Nanofluidics* **19**, 447–456 (2015).
68. Saggiomo, V. & Velders, A. H. Simple 3D Printed Scaffold-Removal Method for the Fabrication of Intricate Microfluidic Devices. *Adv. Sci.* **2**, 1–5 (2015).
69. Gong, H., Woolley, A. T. & Nordin, G. P. High density 3D printed microfluidic valves, pumps, and multiplexers. *Lab Chip* **16**, 2450–2458 (2016).
70. Alam, M. N. H. Z., Hossain, F., Vale, A. & Kouzani, A. Design and fabrication of a 3D printed miniature pump for integrated microfluidic applications. *Int. J. Precis. Eng. Manuf.* **18**, 1287–1296 (2017).
71. Au, A. K., Bhattacharjee, N., Horowitz, L. F., Chang, T. C. & Folch, A. 3D-Printed Microfluidic Automation. *Lab Chip* **15**, 1934–1941 (2015).
72. Keating, S. J. *et al.* 3D printed multimaterial microfluidic valve. *PLoS One* **11**, 1–12 (2016).
73. Au, A. K., Lee, W. & Folch, A. Mail-order microfluidics: evaluation of stereolithography for the production of microfluidic devices. *Lab Chip* **14**, 1294–301 (2014).
74. Monaghan, T., Capel, A. J., Christie, S. D., Harris, R. A. & Friel, R. J. Solid-state additive manufacturing for metallized optical fiber integration. *Compos. Part A* **76**, 181–193 (2015).
75. Monaghan, T., Harding, M. J., Harris, R. A., Friel, R. J. & Christie, S. D. R. 3D printed microfluidics for integrated analysis and optimisation. *Lab Chip* **16**, 3362–3373 (2016).
76. Capel, A. J. *et al.* 3D printed fluidics with embedded analytic functionality for automated reaction optimisation. *Beilstein J. Org. Chem.* **13**, 111–119 (2017).
77. Hampson, S. M., Rowe, W., Christie, S. D. R. & Platt, M. 3D printed microfluidic device with integrated optical sensing for particle analysis. *Sensors Actuators, B Chem.* **256**, 1030–1037

- (2018).
78. Bishop, G. W., Satterwhite-Warden, J. E., Bist, I., Chen, E. & Rusling, J. F. Electrochemiluminescence at Bare and DNA-Coated Graphite Electrodes in 3D-Printed Fluidic Devices. *ACS Sensors* **1**, 197–202 (2016).
 79. Ambrosi, A., Moo, J. G. S. & Pumera, M. Helical 3D-printed metal electrodes as custom-shaped 3D platform for electrochemical devices. *Adv. Funct. Mater.* **26**, 698–703 (2016).
 80. Chisholm, G., Kitson, P. J., Kirkaldy, N. D., Bloor, L. G. & Cronin, L. 3D printed flow plates for the electrolysis of water: an economic and adaptable approach to device manufacture. *Energy Environ. Sci.* **7**, 3026–3032 (2014).
 81. Azuaje, J. *et al.* An efficient and recyclable 3D printed α -Al₂O₃ catalyst for the multicomponent assembly of bioactive heterocycles. *Appl. Catal. A Gen.* **530**, 203–210 (2017).
 82. Tubío, C. R. *et al.* 3D printing of a heterogeneous copper-based catalyst. *J. Catal.* **334**, 110–115 (2016).
 83. Díaz-Marta, A. S. *et al.* Three-Dimensional Printing in Catalysis: Combining 3D Heterogeneous Copper and Palladium Catalysts for Multicatalytic Multicomponent Reactions. *ACS Catal.* **8**, 392–404 (2018).
 84. Skorski, M. R., Esenther, J. M., Ahmed, Z., Miller, A. E. & Hartings, M. R. The chemical, mechanical, and physical properties of 3D printed materials composed of TiO₂-ABS nanocomposites. *Sci. Technol. Adv. Mater.* **17**, 89–97 (2016).
 85. Avril, A. *et al.* Continuous flow hydrogenations using novel catalytic static mixers inside a tubular reactor. *React. Chem. Eng.* **2**, 180–188 (2017).
 86. Lefevre, J., Gysen, M., Mullens, S., Meynen, V. & Van Noyen, J. The benefit of design of support architectures for zeolite coated structured catalysts for methanol-to-olefin conversion. *Catal. Today* **216**, 18–23 (2013).
 87. Michorczyk, P., Hędrzak, E. & Węgrzyniak, A. Preparation of monolithic catalysts using 3D printed templates for oxidative coupling of methane. *J. Mater. Chem. A* **4**, 18753–18756 (2016).
 88. Manzano, J. S., Weinstein, Z. B., Sadow, A. D. & Slowing, I. I. Direct 3D Printing of Catalytically Active Structures. *ACS Catal.* **7**, 7567–7577 (2017).
 89. Melchels, F. P. W., Feijen, J. & Grijpma, D. W. A review on stereolithography and its applications

- in biomedical engineering. *Biomaterials* **31**, 6121–30 (2010).
90. Murphy, S. V. & Atala, A. 3D bioprinting of tissues and organs. *Nat. Biotechnol.* **32**, 773–785 (2014).
 91. DiMasi, J. A., Grabowski, H. G. & Hansen, R. W. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J. Heal. Econ.* **47**, 20–33 (2016).
 92. Zhang, B. & Radisic, M. Organ-on-a-chip devices advance to market. *Lab Chip* **17**, 2395–2420 (2017).
 93. Ho, C. M. B., Ng, S. H., Li, K. H. H. & Yoon, Y.-J. 3D printed microfluidics for biological applications. *Lab Chip* **15**, 3627–3637 (2015).
 94. Johnson, B. N. *et al.* 3D Printed Nervous System on a Chip. *Lab Chip* **16**, 1393–1400 (2016).
 95. Liu, J., Hwang, H. H., Wang, P., Whang, G. & Chen, S. Direct 3D-printing of cell-laden constructs in microfluidic architectures. *Lab Chip* **16**, 1430–1438 (2016).
 96. Anderson, K. B., Lockwood, S. Y., Martin, R. S. & Spence, D. M. A 3D printed fluidic device that enables integrated features. *Anal. Chem.* **85**, 5622–5626 (2013).
 97. Erkal, J. L. *et al.* 3D printed microfluidic devices with integrated versatile and reusable electrodes. *Lab Chip* **14**, 2023–32 (2014).
 98. LaBonia, G. J., Lockwood, S. Y., Heller, A. A., Spence, D. M. & Hummon, A. B. Drug penetration and metabolism in 3-dimensional cell cultures treated in a 3D printed fluidic device: Assessment of irinotecan via MALDI imaging mass spectrometry. *Proteomics* **16**, 1814–1821 (2016).
 99. Lockwood, S. Y., Meisel, J. E., Monsma, F. J. & Spence, D. M. A Diffusion-Based and Dynamic 3D-Printed Device That Enables Parallel in Vitro Pharmacokinetic Profiling of Molecules. *Anal. Chem.* **88**, 1864–1870 (2016).
 100. Liu, Y., Chen, C., Summers, S., Medawala, W. & Spence, D. M. C-peptide and zinc delivery to erythrocytes requires the presence of albumin: implications in diabetes explored with a 3D-printed fluidic device. *Integr. Biol.* **7**, 534–543 (2015).
 101. Santangelo, M. F., Libertino, S., Turner, A. P. F., Filippini, D. & Mak, W. C. Integrating printed microfluidics with silicon photomultipliers for miniaturised and highly sensitive ATP bioluminescence detection. *Biosens. Bioelectron.* **99**, 464–470 (2018).

102. Singh, M. *et al.* 3D printed conformal microfluidics for isolation and profiling of biomarkers from whole organs. *Lab Chip* **17**, 2561–2571 (2017).
103. Krejcova, L. *et al.* 3D printed chip for electrochemical detection of influenza virus labeled with CdS quantum dots. *Biosens. Bioelectron.* **54**, 421–427 (2014).
104. Costa, P. F. *et al.* Additively Manufactured Device for Dynamic Culture of Large Arrays of 3D Tissue Engineered Constructs. *Adv. Healthc. Mater.* **4**, 864–873 (2015).
105. Knowlton, S. *et al.* 3D-printed microfluidic chips with patterned , cell-laden hydrogel constructs. *Biofabrication* **8**, 25019 (2016).
106. Ong, L. J. Y. *et al.* A 3D printed microfluidic perfusion device for multicellular spheroid cultures. *Biofabrication* **9**, 45005 (2017).
107. Urrios, A. *et al.* 3D-printing of transparent bio-microfluidic devices in PEG-DA. *Lab Chip* **16**, 2287–2294 (2016).
108. Gross, B. C., Anderson, K. B., Meisel, J. E., McNitt, M. I. & Spence, D. M. Polymer Coatings in 3D-Printed Fluidic Device Channels for Improved Cellular Adherence Prior to Electrical Lysis. *Anal. Chem.* **87**, 6335–6341 (2015).
109. Pietrzak, K., Isreb, A. & Alhnan, M. A. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *Eur. J. Pharm. Biopharm.* **96**, 380–387 (2015).
110. Okwuosa, T. C. *et al.* On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. *Eur. J. Pharm. Sci.* **118**, 134–143 (2018).
111. Preis, M. & Öblom, H. 3D-Printed Drugs for Children—Are We Ready Yet? *AAPS PharmSciTech* **18**, 303–308 (2017).
112. Norman, J., Madurawe, R. D., Moore, C. M. V., Khan, M. A. & Khairuzzaman, A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. *Adv. Drug Deliv. Rev.* **108**, 39–50 (2017).
113. Trenfield, S. J., Awad, A., Goyanes, A., Gaisford, S. & Basit, A. W. 3D Printing Pharmaceuticals: Drug Development to Frontline Care. *Trends Pharmacol. Sci.* **39**, 440–451 (2018).
114. Khaled, S. A., Burley, J. C., Alexander, M. R. & Roberts, C. J. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *Int. J. Pharm.* **461**, 105–111 (2014).
115. Kyobula, M. *et al.* 3D inkjet printing of tablets exploiting bespoke complex geometries for

- controlled and tuneable drug release. *J. Control. Release* **261**, 207–215 (2017).
116. Hsiao, W. K., Lorber, B., Reitsamer, H. & Khinast, J. 3D printing of oral drugs: a new reality or hype? *Expert Opin. Drug Deliv.* **15**, 1–4 (2018).
 117. Goyanes, A., Kobayashi, M., Martínez-Pacheco, R., Gaisford, S. & Basit, A. W. Fused-filament 3D printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. *Int. J. Pharm.* **514**, 290–295 (2016).
 118. Skowrya, J., Pietrzak, K. & Alhnan, M. A. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *Eur. J. Pharm. Sci.* **68**, 11–17 (2015).
 119. Smith, D. M., Kapoor, Y., Klinzing, G. R. & Procopio, A. T. Pharmaceutical 3D Printing: Design and Qualification of a Single Step Print and Fill Capsule. *Int. J. Pharm.* **544**, 21–30 (2018).
 120. Goyanes, A., Buanz, A. B. M., Hatton, G. B., Gaisford, S. & Basit, A. W. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. *Eur. J. Pharm. Biopharm.* **89**, 157–162 (2015).
 121. Khaled, S. A., Burley, J. C., Alexander, M. R., Yang, J. & Roberts, C. J. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. *J. Control. Release* **217**, 308–314 (2015).
 122. Acosta-Velez, G. F. & Wu, B. M. 3D Pharming: Direct Printing of Personalized Pharmaceutical Tablets. *Polym. Sci.* **2**, 1–10 (2016).
 123. Alomari, M., Mohamed, F. H., Basit, A. W. & Gaisford, S. Personalised dosing: Printing a dose of one's own medicine. *Int. J. Pharm.* **494**, 568–577 (2015).
 124. Buanz, A. B. M., Saunders, M. H., Basit, A. W. & Gaisford, S. Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing. *Pharm. Res.* **28**, 2386–2392 (2011).
 125. Genina, N. *et al.* Tailoring controlled-release oral dosage forms by combining inkjet and flexographic printing techniques. *Eur. J. Pharm. Sci.* **47**, 615–623 (2012).
 126. Sandler, N. *et al.* Inkjet printing of drug substances and use of porous substrates-towards individualized dosing. *J. Pharm. Sci.* **100**, 3386–3395 (2011).
 127. Genina, N., Fors, D., Palo, M., Peltonen, J. & Sandler, N. Behavior of printable formulations of loperamide and caffeine on different substrates—Effect of print density in inkjet printing. *Int. J.*

- Pharm.* **453**, 488–497 (2013).
128. Stern, M. *et al.* Additive Manufacturing of Optically Transparent Glass. *3D Print. Addit. Manuf.* **2**, 92–105 (2015).
 129. Kotz, F. *et al.* Three-dimensional printing of transparent fused silica glass. *Nature* **544**, 337–339 (2017).
 130. Nguyen, D. T. *et al.* 3D-Printed Transparent Glass. *Adv. Mater.* **29**, 1–5 (2017).
 131. Ji, Q. *et al.* A Modular Microfluidic Device via Multimaterial 3D Printing for Emulsion Generation. *Sci. Rep.* **8**, 1–11 (2018).
 132. Rocha, V. G. *et al.* Multimaterial 3D Printing of Graphene-Based Electrodes for Electrochemical Energy Storage Using Thermoresponsive Inks. *ACS Appl. Mater. Interfaces* **9**, 37136–37145 (2017).

Acknowledgments

Authors would like to acknowledge the support of Loughborough University School of Sport, Exercise and Health Science and School of Science. This work was part funded by the Engineering and Physical Sciences Research Council (EPSRC) grant REF: EP/ L02067X/2.

Contributions

All authors contributed equally to the research, writing and review of this article.

Competing interests

The authors declare no competing interests.

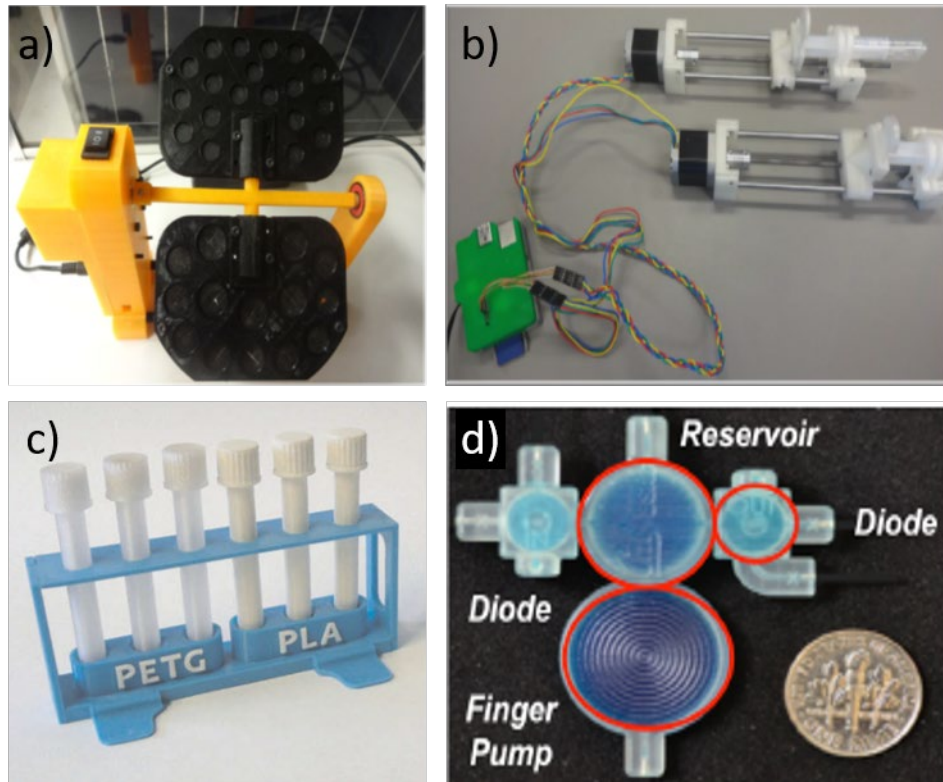


Fig 1. Examples of 3D printed laboratory hardware A) An open source laboratory sample rotator mixer/shaker combination.⁴ B) An open source syringe pump.⁶ C) PETG and PLA printed test tubes and rack.⁹ D) Modular finger actuated microfluidic pump.⁸

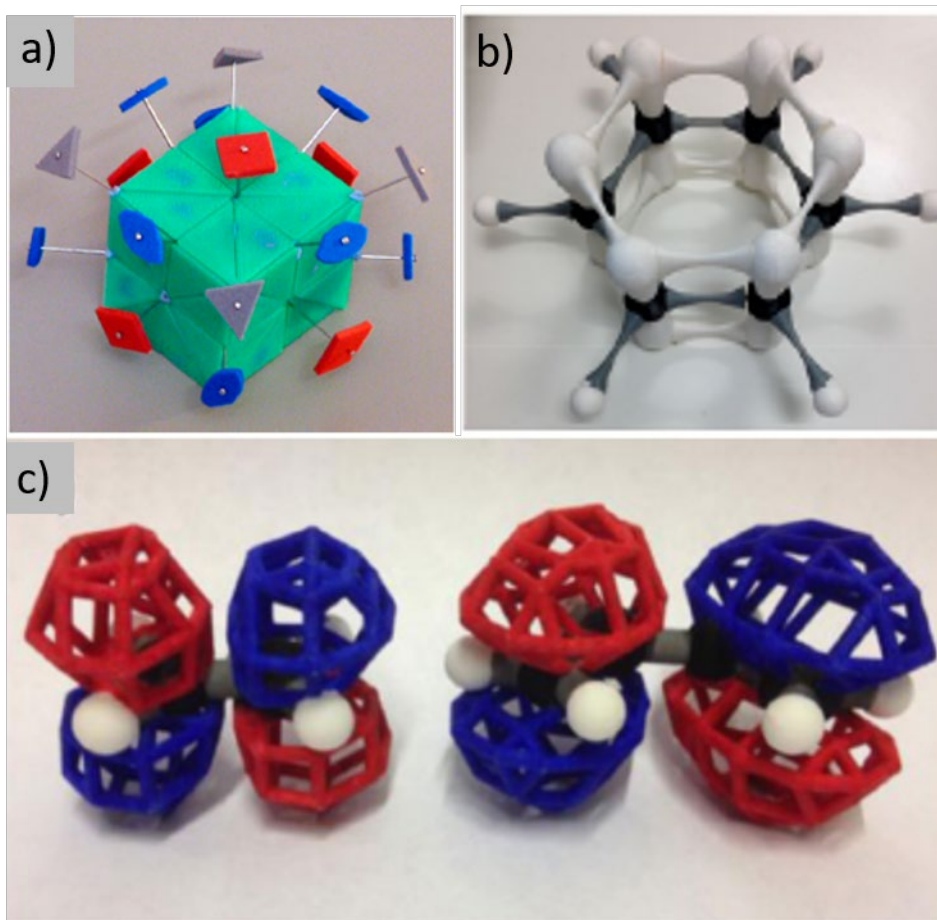


Fig 2. Examples of 3D printed model kits **A)** Dissection puzzle of a cube used as a teaching aid for crystal symmetry and point groups.³⁴ **B)** Model of benzene showing the π -cloud of the double bonds and the π -cloud conjugation.²⁸ **C)** Molecular orbitals for the lowest unoccupied molecular orbital (LUMO) of ethene and the highest occupied molecular orbital (HOMO) of 1,3-butadiene.³³

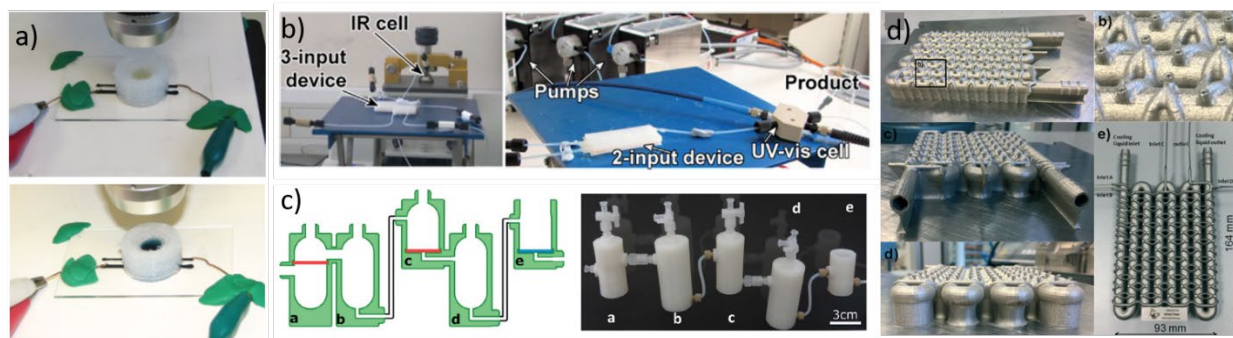


Fig 3. Examples of 3D printed micro- and millifluidics **A)** Electrochemical flow cell using printed conductive acetoxy-silicone/carbon black composite electrodes.⁴⁴ **B)** In-line spectroscopic flow cells connected to a printed fluidic device. **C)** Modular reaction cartridges used for the synthesis of (\pm) baclofen.⁴⁸ **D)** High temperature and pressure resistant stainless steel flow reactor.⁵⁹

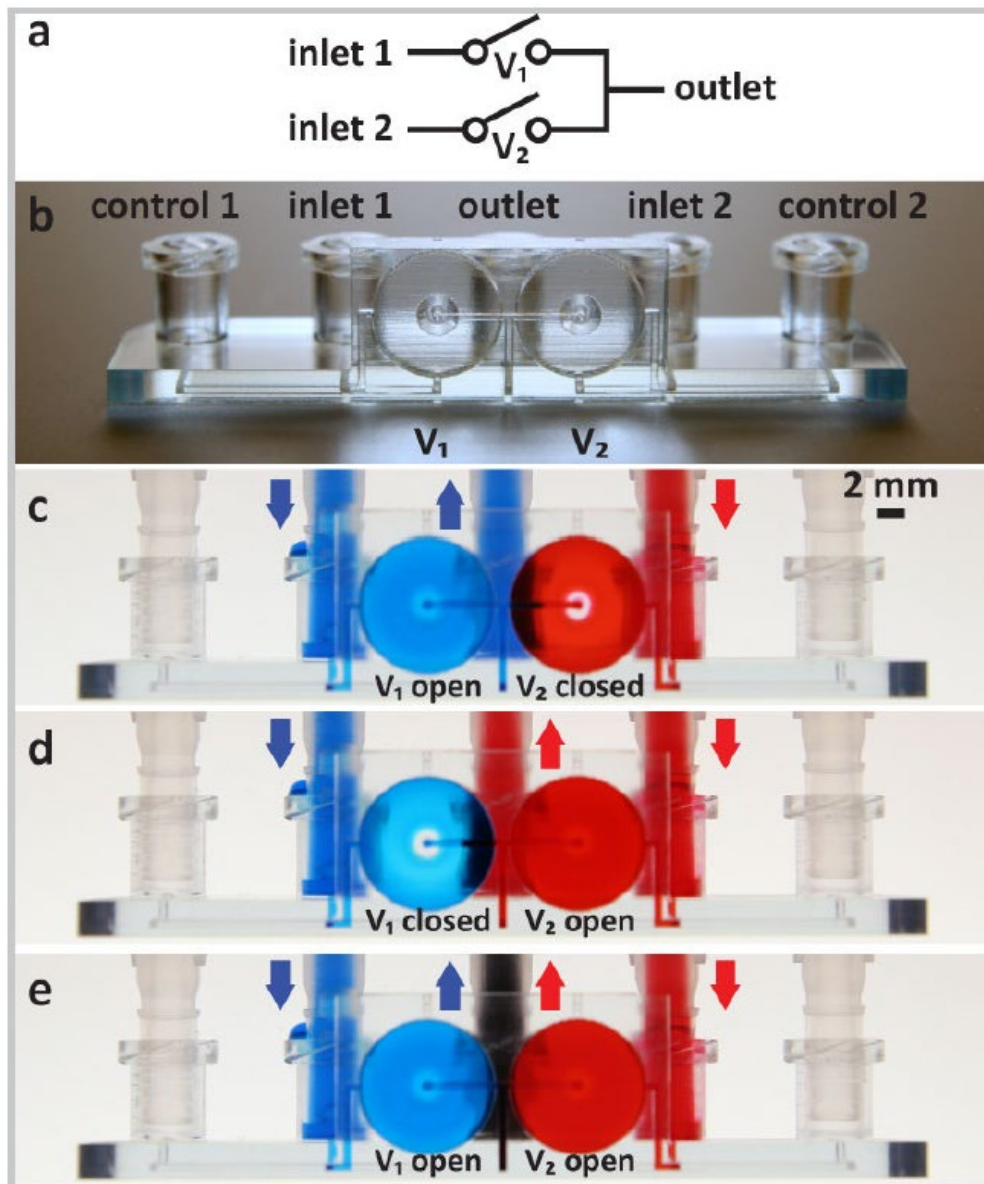


Fig 4. Example of a 3D printed switching valve A) Circuit diagram for the valve B) Photograph of the switching valve C-E) Photographs of the switch in each of its different actuation states.⁶⁸

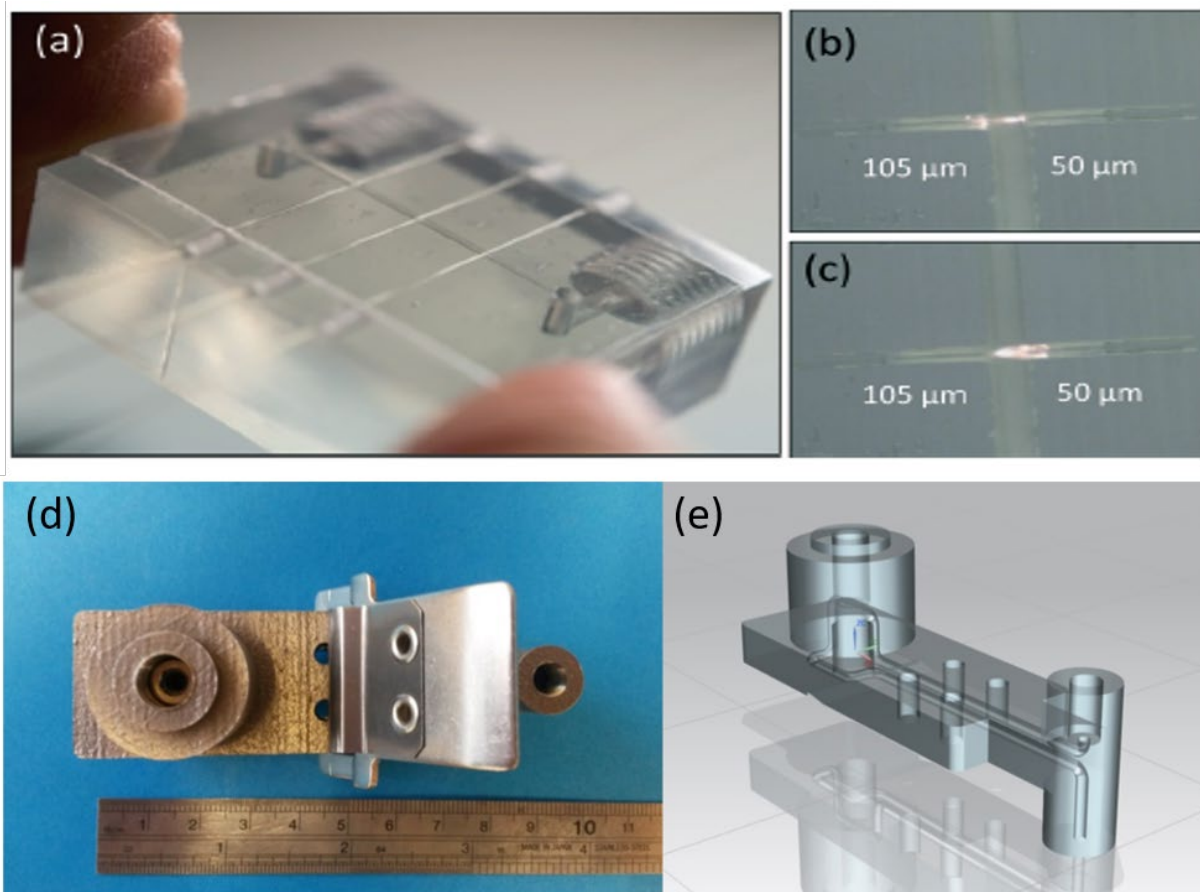


Fig 5. Examples of 3D printed micro- and millifluidics with embedded technology A-C) Microfluidic channel embedded with 50 and 105μm optical fibres.⁷¹ D-E) Millifluidic flow device printed from Ti-6Al-4V alloy with embedded spectroscopic viewing window.⁷²

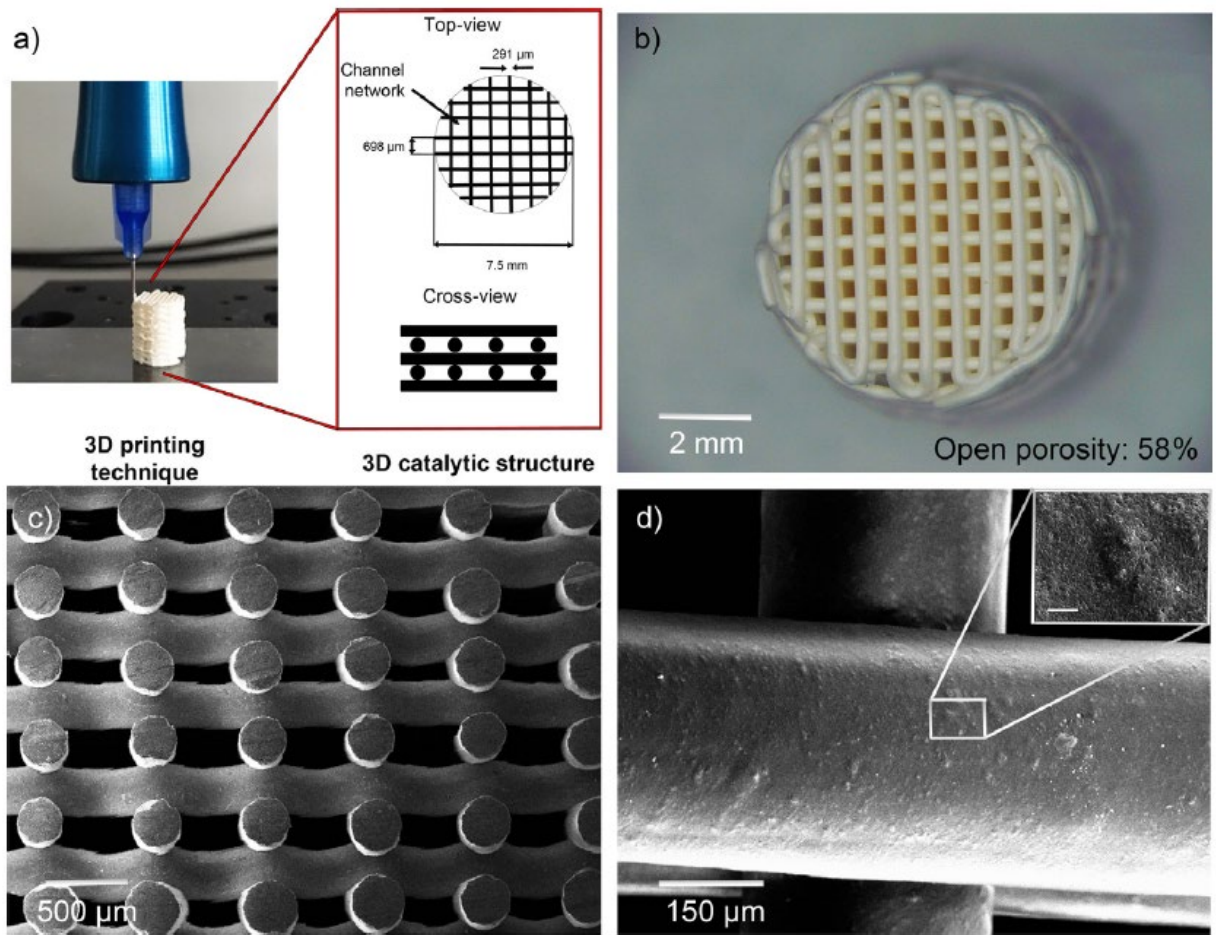


Fig 4. Example of a 3D printed catalytic structure **A)** Printing of the Al_2O_3 catalytic structure **B)** Final sintered structure **C)** Cross-sectional SEM of the structure **D)** Surface filament view of the sintered structure.⁷⁷

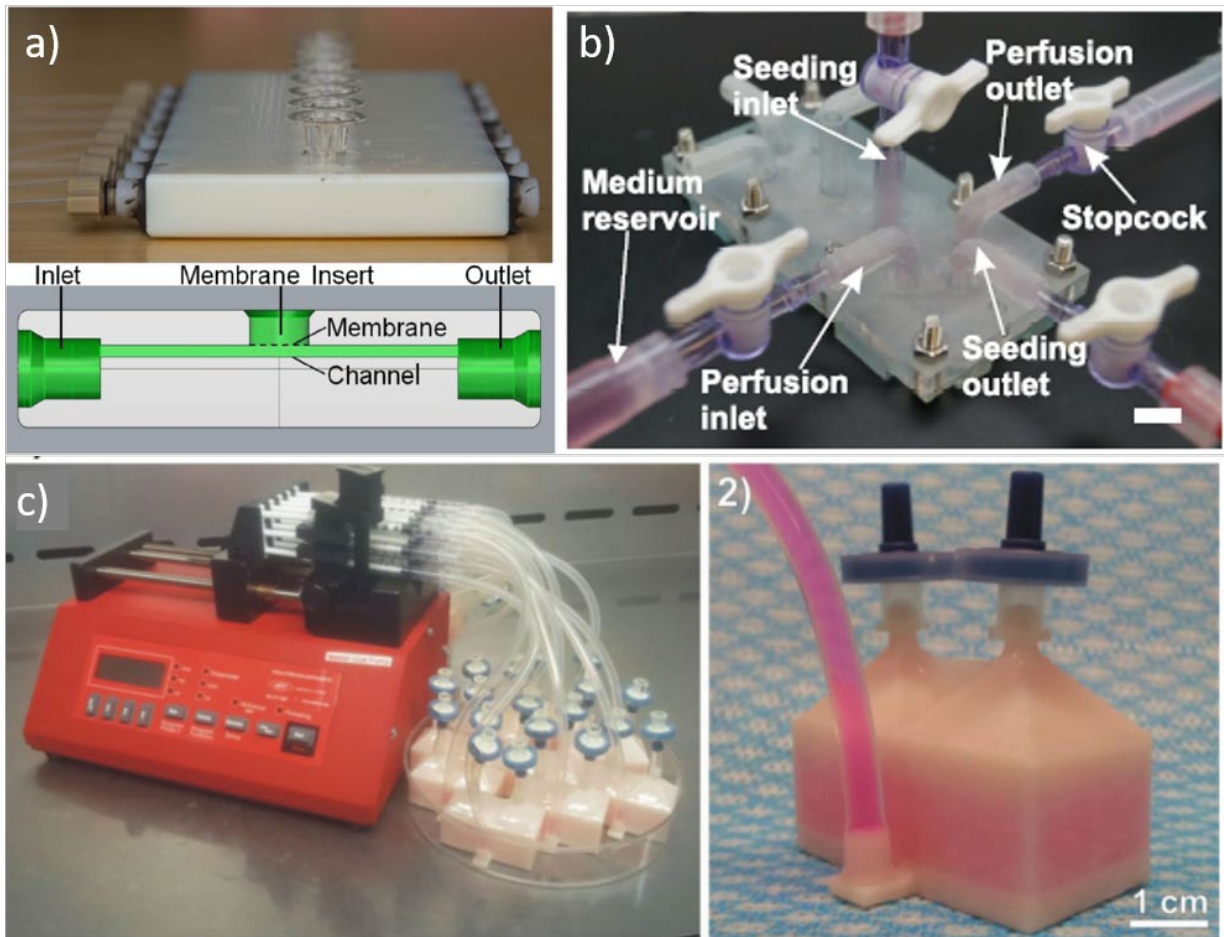


Fig 5. Examples of 3D printed biological perfusion reactors A) Biological perfusion system with integrated cell culture membrane inserts.⁹¹ B) Microfluidic multicellular spheroid culture system.¹⁰¹ C-D) Multiple 3D printed cell culture devices connected to a single syringe pump for dynamic culture of large arrays.⁹⁹

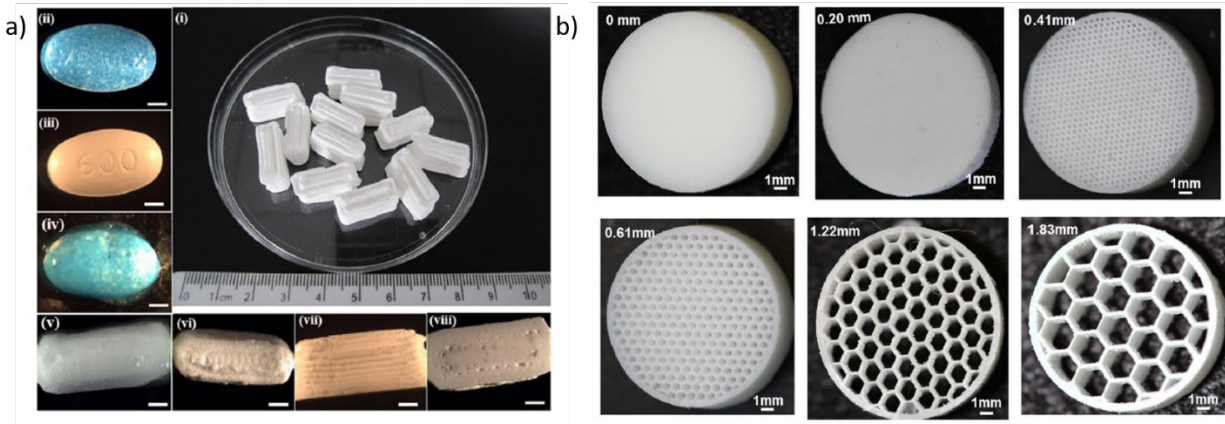


Fig 6. Examples of 3D printed pharmaceutical tablets A) Various guafenesin bilayer tablets and their dissolution products.¹⁰⁹ B) Tablets printed with both solid and honeycomb architectures for controlled and tuneable drug release.¹¹⁰