Trends in Biotechnology

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Opinion

Enabling Microfluidics: from Clean Rooms to Makerspaces

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The traditional requirement for clean rooms and specialized skills has inhibited many biologists from pursuing new microfluidic innovations. Makerspaces provide a growing alternative to clean rooms: they provide low-cost access to fabrication equipment such as laser cutters, plotter cutters, and 3D printers; use commercially available materials; and attract a diverse community of product designers. This Opinion discusses the materials, tools, and building methodologies particularly suited for developing novel microfluidic devices in these spaces, with insight into biological applications and leveraging the maker community. The lower barrier to access of makerspaces ameliorates the otherwise poor accessibility and scalability of microfluidic prototyping.

Trends

The use of simple tools and materials to manufacture microfluidic devices provides an opportunity for makerspaces to serve as a hotbed for microfluidic device development.

Materials such as plastic, adhesive, and paper, along with tools such as plotter/laser cutters and 3D printers, enable building integrated microfluidic systems that are more easily translated to large-scale manufacturing.

Makerspaces provide low-cost access to prototyping tools and access to technically diverse human capital, and they enable those without advanced skills to participate in microfluidic device development.

Microfluidics and the Market

Over the past few decades, thousands of novel microfluidic **point-of-care** (**POC**, see Glossary) diagnostic platforms and applications have been published in peer-reviewed journals; however, a low percentage have reached market [1]. Even with large investments from government and industry in both Europe and North America, surprisingly few **lab-on-a-chip (LOC)** microfluidic diagnostic tests have translated to commercial products [2]. This discrepancy somewhat constrains the potential market for these devices, which is expected to grow from $1.6 billion in 2013 to $3.6–5.7 billion by 2018; the key driver of this growth is the need for early detection and personalized treatment of lifestyle diseases, which have become more prominent within a growing geriatric population [3,4].

Thus far, the field of POC microfluidic diagnostics has been predominantly addressed in academia with **polydimethylsiloxane (PDMS)** devices manufactured using **soft lithography** techniques, originally popularized by the Whitesides group [5,6]. A brief review of soft lithography microfluidics is presented in Box 1 [6–15]. The focus of this Opinion is the discussion of microfluidic prototyping that takes place in makerspaces rather than clean rooms. Alternative rapid prototyping methods that take advantage of these materials for microfluidics have been reviewed previously [16]. For example, laser cutting can be used to cut microfluidic channels in double-sided pressure sensitive adhesive (PSA) [17], to directly ablate microfluidic channels in polymer materials [18], and even to create molds for PDMS from laser cut adhesive [19]. Plotter cutting, also known as **xurography**, uses a drag knife printer to cut microfluidic designs from laminate and masking films [20–22]. Xurography has even been used to directly cut microfluidic channels in PDMS and cyclic olefin copolymer films [23,24]. 3D printing technologies have also begun to show promise for microfluidic device fabrication [25–27]. While these methods do not provide the superior resolution of photolithographic methods, the use of plastic, paper, and laminate substrates are more translatable to scalable manufacturing methods – such as die

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Box 1. Soft Lithography Microfluidics – Pros and Cons

Soft lithography methods for microfluidics create master molds from photolithography techniques followed by curing of a pre-polymer (PDMS) on top of the mold master, where after curing, a PDMS-negative stamp of the mold is created and bonded irreversibly to glass (see Figure 1 in main text). Soft lithography techniques have proven useful in microfluidics under a wide range of applications from channel fabrication to pattern generation [7]. The key benefit of soft lithography methods is the ability to rapidly prototype [8]. The technique is ideal for biological applications because the feature resolution can match the micrometer and even nanometer feature sizes often found in biology. The PDMS polymer provides an ideal candidate for microfluidic devices as it is nontoxic, widely available, transparent, hydrophobic, gas-permeable, and elastomeric [6,9]. Oxidized PDMS surfaces can be irreversibly bonded together by a spontaneous dehydration of SiOH groups, and PDMS can be passivated and functionalized through various chemistries for high-efficiency molecular assays. The flexibility of the PDMS polymer enables a wide variety of geometries, layering, and unit operations applicable to a plethora of unique microfluidic manipulations [6].

By contrast, the photolithography and soft lithography methods used to create these devices suffer from the nature of artisanal and resource-consuming processes (pour, cure, cut, punch, and bond) as opposed to the traditional industry-standard injection molding process, where a mold is filled, the polymer is rapidly cured, and the part is ejected. Contract manufacturers, such as FlowJEM (Ontario, Canada) and SIMTech Microfluidics Foundry (Singapore), also perform soft lithography prototyping and can provide custom molds for a fee ($100–200 for a single layer SU-8 mold depending on the design); however, the design process is slowed down waiting for molds to be manufactured and shipped. While PDMS devices may be well suited for the research setting, the lack of scalability in soft lithography and the high cost of PDMS (relative to cost-efficient thermoplastics) has limited commercial potential [10]. A technology map developed by Chin *et al.* shows how virtually none of the major players in the microfluidic *in vitro* diagnostics market use PDMS in their products, instead leaning towards plastic, glass, or paper materials, which can be more easily mass-manufactured through processes such as injection molding, casting, and die cutting respectively [11]. These common manufacturing materials and methods offer additional benefits such as standardization of fabrication, improving quality control, and better integration with other parts made of similar material [11,12]. A wide variety of advances in microfluidics manufacturing, materials, functions, and operations have yielded a powerful toolkit to enable plastic microfluidic development for a plethora of applications [13–15].

cutting, hot embossing, and injecting molding – to translate a finished prototype into a commercial product. An example of a rapid prototyping method amenable to scaled-up manufacturing is laser cutting. Figure 1 shows a comparison of device prototyping using soft lithography methods versus laser cutting of plastics, laminates, and paper.

Makerspaces, DIY Biology, and Integrated Thinking

The investigation of these alternative materials is well suited for exploration in the emerging ecosystem of community makerspaces [28]. In the broadest sense, makerspaces are physical spaces, usually accessible to the public, where communities are able to access tools – spanning additive and subtractive techniques – for fabricating almost anything [29]. Such spaces can be formalized as part of an organization like the Fab Lab network (www.fabfoundation.org), or more informally organized. With >1000 active spaces around the world, makerspaces have lowered the barrier to accessing fabrication technologies, enabling the exploration of microfluidic rapid prototyping techniques reviewed in this work.

In the past several years, there has also been a growing movement of **'do-it-yourself' (DIY) biology** and similar emergence of bio-makerspaces [30], which typically feature tools and basic infrastructure for conducting molecular biology and microbiology projects. As the majority of applications for microfluidics have involved biological systems, we believe the reviewed techniques will also be of interest, and accessible, to DIY biology communities as well.

A key factor in the shift of microfluidic manufacturing from traditional photolithographic methods to 'maker manufacturing' is the push for fully integrated microfluidic systems that can be readily translated to industry. A major roadblock for lab-on-a-chip devices is plugging and sealing the device to all the interfaces needed (e.g., detection, electric manipulation, and inlets/outlets) [31]. For example, Lafluer *et al.* used 3D-printed and paper substrates to develop an entirely integrated sample-to-result nucleic acid amplification test [32]. Kinahan *et al.* used laser-cut

Glossary

Contract manufacturer: a company that is used to outsource a manufacturing task. In microfluidics, contract manufacturers are commonly used to build device molds for labs without a clean room or provide device components made from tools such as CNC mills or laser cutters.
Do-it-yourself (DIY) biology: a user-based community of individuals or small organizations that study biology and life science outside the traditional academic setting, typically for education, hobbyist, or entrepreneurship applications.
Double-sided tape: a material that is composed of a carrier layer such as a film or tissue where adhesive material has been coated on both sides. These tapes are typically thicker than transfer tapes.
Droplet microfluidics: devices that create highly monodisperse droplets from two-phase flow, such as droplets of water in oil. For example, individual cells from a sample can be trapped and sorted in droplets based on a wide variety of characteristics.
***In vitro* transcription/translation:** The process of using bacterial lysate and other cellular machinery outside the cell environment to transcribe and translate native or synthetic DNA into its coded protein. For example, this process could be used to test a patient's specific HIV virus sequence for drug resistance by testing drug response of the corresponding coded HIV protease.
Isothermal PCR: a variation of traditional nucleic acid amplification (PCR) that requires no heating cycles for amplification, reducing the need for bulky and expensive equipment.
Lab on a chip (LOC): a device that miniaturizes one or multiple functions of a laboratory, enabling automated, high-throughput characterization of biological samples, which could potentially replace traditional lab testing.
Lateral flow assay: a simple paper-based device where a sample is flowed along a paper strip and over a detection region where a colorimetric or fluorescent signal is given with intensity scaling with target analyte concentration. The best-known lateral flow assay application is the home pregnancy test.

acrylic and double-sided PSA to develop an integrated biplex liver assay [33]. These technologies show off the power of simple devices that anyone can make and rapidly scale to bulk manufacturing. To enable others to take part in this type of product design and development, we review the materials and tools used by current researchers to develop these platforms.

Maker Microfluidics Manufacturing

This section reviews the development of microfluidic platforms using simple materials and manufacturing equipment often found in makerspaces. While microfluidics can be made from a wide variety of materials and methods, this Opinion focuses on plastics, adhesives, and paper substrates, with a brief discussion of the promise of 3D-printed microfluidics.

Materials

Plastics are a popular material choice for microfluidics as they collectively offer a wide variety of desirable properties including optical clarity, solvent resistance, and scalable manufacturing methods, which have been reviewed previously [34]. Studies have shown promise for polymeric materials with regard to biocompatibility [35], surface modification and integration of functional materials [36], and material autofluorescence [37,38]. Acrylic is one of the simplest and most useful plastics for the makerspace because of its low cost, high optical clarity, wide availability, and compatibility with a wide variety of manufacturing tools such as laser cutters. Similar plastics, such as polycarbonate, may be desired for even greater optical clarity and standardization in large-scale manufacturing; however, polycarbonate cannot be cut on a conventional laser cutter, and specialty **contract manufacturers**, such as Axxicon (http://axxicon.com), often require large bulk orders to make a profit. For spaces without a laser cutter, materials can be shipped precut by laser cutting services such as Ponoko (www.ponoko.com) at a low cost with no minimum order. For example, a custom pre-laser-cut sheet of 800 mm × 400 mm clear acrylic (1.5 mm thickness) costs approximately $50 plus shipping.

Cut double-sided adhesive tapes are ideal materials for bonding microfluidic architecture to substrates. Laser-cut microchannels in adhesive tape can be sandwiched between two pieces of plastic with access ports to serve as liquid reservoirs for a wide variety of biological applications such as a cell sorter for stem cells, a mammalian cell chemostat, a cytotoxicity assay system, and even *in vitro* organ models [39]. Selecting a tape adhesive can be a daunting task considering the expansive selection from companies such as 3M (www.3m.com) and Adhesives Research (www.adhesivesresearch.com). The key considerations for selecting a tape are: (i) fabrication considerations; (ii) tape thickness; and (iii) cost/availability. For fabricating a plastic device held together by double-sided thin-film adhesive, cutting microfluidic channels into the adhesive can be challenging if the product is not double lined, meaning both sides of the adhesive have a removable liner. While **tape converter** companies such as Converters Inc. (www.converters.com) offer to add a second liner, large minimum orders can be cost prohibitive. Converters can be avoided by purchasing tapes that already come with liner on both sides. Another consideration for adhesive selection is choosing between a **transfer tape** and a **double-sided tape**. Transfer tapes are entirely composed of adhesive material whereas traditional double-sided adhesive have a carrier layer coated on both sides with adhesive. Thus, transfer tapes are typically better suited for thinner applications (<50 μm) such as cellular and biochemical assays where reagent may be expensive, whereas double-sided adhesives are suited for thicker applications (50–200 μm), such as cell culture where media may need to be slowly perfused over cells with low shear. A final consideration is the cost and availability of the desired adhesive as the minimum order direct from 3M or Adhesives Research are typically on the range of 1500 foot rolls and can cost upwards of $10 000. Often, free samples of certain products are available or their products can be purchased in smaller amounts from distributors such as Grainger (www.grainger.com) and Amazon.com (www.amazon.com) depending on availability. Table S1 in the supplementary material online contains a list of adhesives appropriate for microfluidics.

Plotter cutter: also known as a vinyl cutter, this computer-controlled machine controls the movement of a sharp blade over a thin material to cut out shapes. In microfluidics, plotter cutters can be used to cut channel architecture out of paper or thin-film adhesive for device manufacturing.

Point of care (POC): in reference to microfluidics, POC means deployable at the site where a patient is treated. This paradigm is in contrast to laboratory tests in which biological samples are collected at the treatment site and sent to a dedicated laboratory for testing. The key benefit of POC microfluidics is the ability for more rapid diagnosis or treatment.

Polydimethylsiloxane (PDMS): a silicon-based organic polymer that is popular for rapid prototyping of microfluidic devices due to its beneficial properties of flexibility, device bonding, optical clarity, and biocompatibility.

Soft lithography: a technique where an elastomeric material (such as PDMS) is poured over a structure-patterned mold to produce a product such as a lab on a chip.

Tape converter: a company that modifies a commercially produced adhesive with processes such as die cutting or adding a second liner to a single lined tape. Typically these companies require a large minimum order for their services.

Transfer tape: materials that are entirely composed of pressure sensitive adhesive material (without a carrier). These are typically thinner than double-sided tape.

Xurography: the use of a programmable drag knife to cut structures out of a material to produce patterns or channels. In contract to laser cutting, xurography is a style of contact cutting that can cause material shearing but will typically avoid burn products from material ablation.

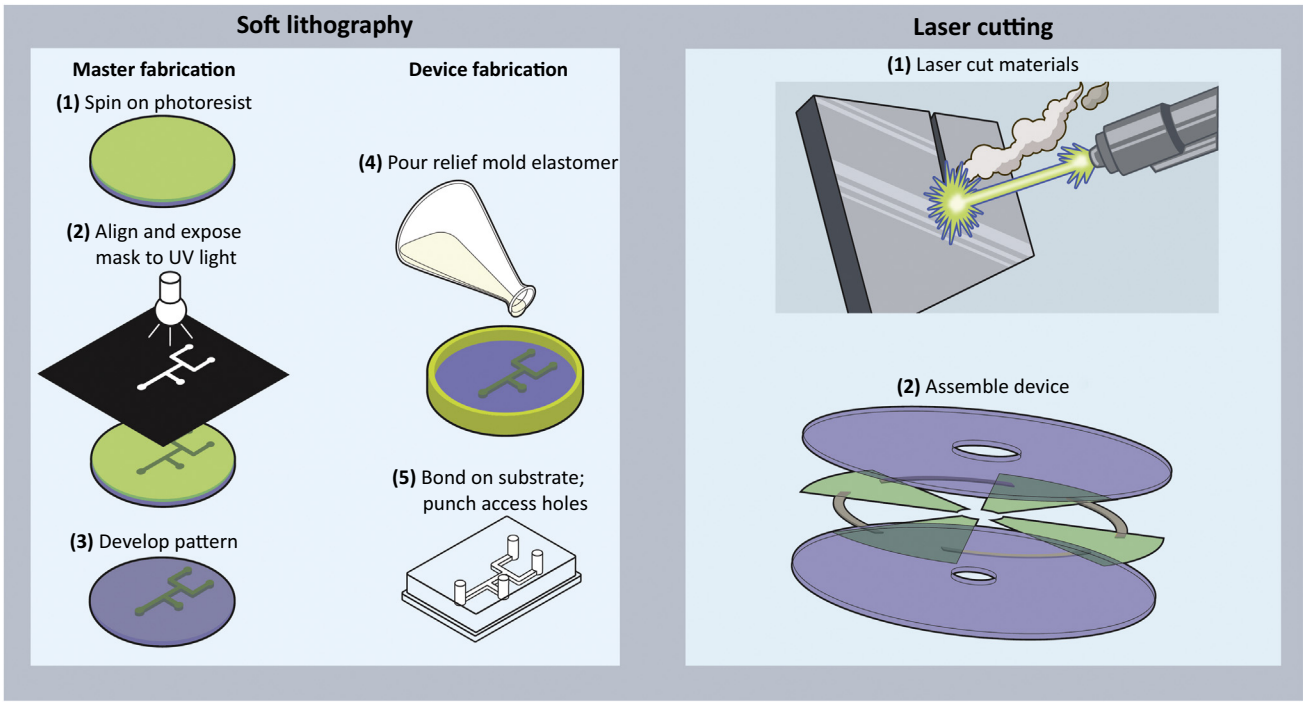

Figure 1. Rapid Prototyping Using Soft Lithography versus Laser Cutting. (Left) The multistep process of soft lithography, wherein first a master mold is developed followed by curing a prepolymer substrate above, peeling off, bonding to a substrate, and punching access holes. (Right) The more straightforward process of laser cutting all device parts followed by lamination or thermal bonding to assemble a device.

Paper substrates gained renewed popularity in 2004 when the World Health Organization (WHO) declared specific performance criteria for developing POC, ultra-low-cost diagnostics in low-resource settings [40]. Which paper substrate is most appropriate depends on the context for its use in applications, which include nucleic acid and protein separation, immunoassays, and even cell culture [41–44]. GE Healthcare Life Sciences' Whatman line (www.gelifesciences.com) offers a wide variety of paper substrates with thicknesses appropriate for integration into plastic/tape microfluidics and stand-alone devices. Table S2 in the supplementary material online contains a list of all of the paper substrates used by the authors along with comments to best help guide paper selection.

Tools

Laser and plotter cutting are two simple methods for cutting microfluidic channels in plastic, paper, and tape. Both of these methods are similar in workflow, feeding in a substrate to be cut by either a laser or knife. Laser cutters have the benefit of noncontact cutting and higher resolution. These benefits come at the expense of higher capital equipment costs, the requirement for a vacuum pump to clear out debris and fumes, and potential burn residue created during the cutting [45]. While material leaching of plastics and adhesives may pose problems for some sensitive biological assays, often burn products from laser cutting of particular materials have been shown to inhibit reactions such as polymerase chain reaction (PCR) [46]. **Plotter cutters** (also commonly referred to as vinyl cutters or cutting plotters) are significantly cheaper, require no pumping system, and leave no burn residues. With the growing popularity of makerspaces in both academia and industry, many facilities now have these capabilities already available in a shared space. While other works directly compare results from these two cutting tools for microfluidics [45], Table S3 in the supplementary material online highlights the key differences between laser and plotter cutting.

Bridging applications

Before moving ahead to device design and prototyping, the first job is to identify which materials and tools best suit the biological application. We recommend keeping device design as simple as possible to avoid unnecessary sources of error that may invalidate an assay (e.g., too many individual steps). The simplest material for developing a device is often paper as its ability to be cut and directly wax printed enables a variety of fluidic manipulations and assays to be performed. Paper has particular strengths for POC diagnostic immunoassays (i.e., **lateral flow assays**), PCR (i.e. **isothermal PCR**, sample preparation), and even for synthetic biology applications such as ***in vitro* transcription/translation**. A primary weakness of paper is its opacity, which can occlude a weak signal from a fluorescent/colorimetric reporter and limit visual analyses. By contrast, devices made from double-sided PSA with cut microfluidic channels sandwiched between plastic provide superior signal-to-nose ratios for fluorescent or colorimetric readouts as well as potential for high multiplexing through **droplet microfluidic** devices. Plastic and tape devices provide a viable platform for cellular assays, such as counting $CD4^+$ T cells for HIV diagnostics from whole blood, immunophenotyping invasive cell types in vitreous fluid for ocular diagnostics, and isolating stem cells from a patient. Finally, for devices that may still require the beneficial properties of PDMS, such as gas-controlled cell chemostats, molds created from laser-cut plastic, or even 3D-printed materials, can be used in place of traditional photolithography molds, although with the cost of reduced resolution.

Methodology

A simple and enabling methodology for maker microfluidics is design–cut–assemble, shown schematically in Figure 2. This method streamlines rapid prototyping of microfluidic devices using plastics, paper, and adhesive substrates, and can be appropriately edited to incorporate different materials and technologies [47]. While more traditional material combinations such as a plastic-adhesive device may seem like an easy first step, more creative solutions may also be more efficient, such as a paper-adhesive microfluidic origami device [48]. Once the materials are chosen, a computer-aided design (CAD) file must be designed to guide the cutting process. Next, the substrates need to be cut using methods such as laser and plotter cutting. While this opinion focuses on laser and plotter cutting, wax printing and Computer Numeric Control (CNC) micromilling are viable alternatives. Briefly, wax printing methods are a popular and simple way to create hydrophobic patches on paper substrates to create microfluidic architecture [49]. Devices can be made as simply as using a wax-based ink printer and a hot plate to set the wax into the paper. CNC-micromilling can also be used to directly drill channels in plastic or drill a mold for PDMS casting [50]. Finally, once all of the parts are cut, assembly is typically completed by a manual process such as lamination, thermal bonding, or folding. A set of considerations for each step of this process is shown in Box 2.

3D Printing

While design–cut–assemble is a powerful process for maker microfluidics, makerspaces offer other enabling technologies for microfluidic manufacturing. One of the most ubiquitous technologies in makerspaces is 3D printing, which has been referred to as the start of a revolution in microfluidics [27]. While many devices have been developed, there are still inherent challenges faced by makerspace-available systems such as low optical clarity and material leaching [51]. These challenges are being rapidly overcome by new 3D-printing technologies such as Dolomite's Fluidic Factory, which can produce leak-proof devices within 20 min, made from clear, biocompatible cyclic olefin copolymer instead of traditional resins. While these printing technologies further develop to produce fully integrated microfluidic platforms, current technologies can be used to fabricate complementary microfluidic components, such as 3D-printed spinners for centrifugal devices, alignment rigs for multilayered device building, and even common laboratory equipment [52]. These tools are just as important as the microfluidics themselves to produce a complete system that replaces expensive engineering equipment,

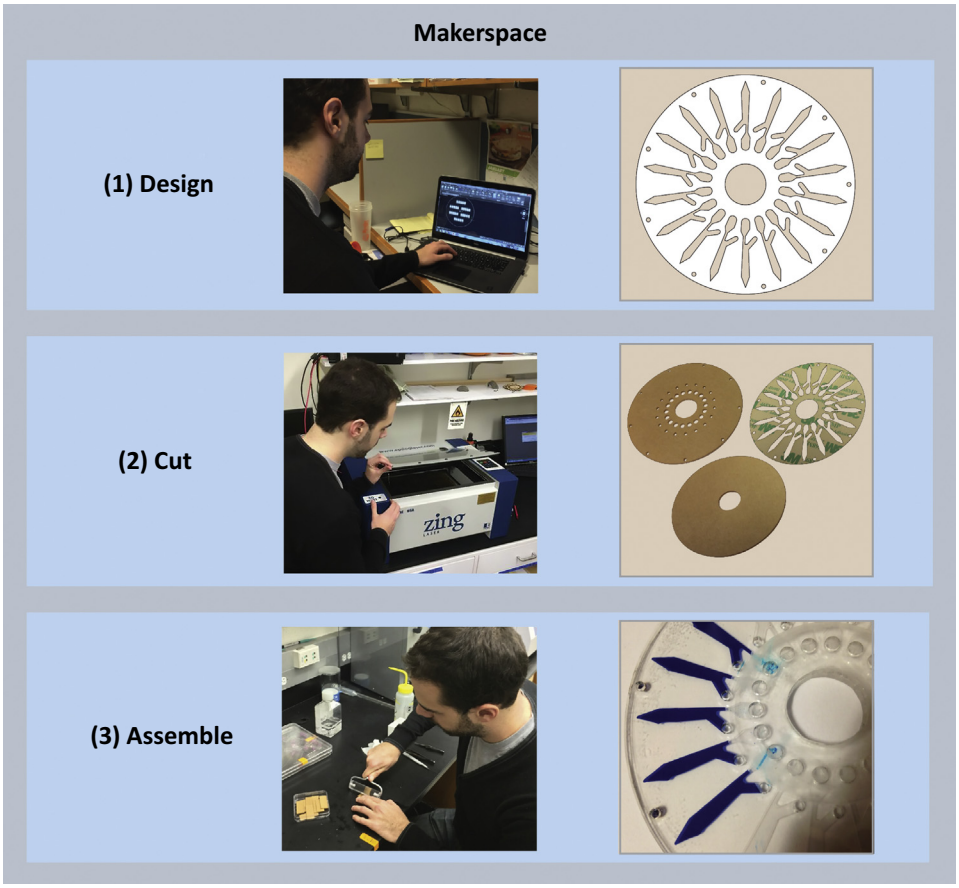

Figure 2. Design–Cut–Assemble Methodology. Designing device parts in computer-aided design, cutting them out using a laser or plotter cutter, and assembling with lamination.

such as syringe pumps and custom fluidic locking connectors. Additionally, the design files for such complementary hardware can be easily shared via repositories such as Thingiverse (www.thingiverse.com) and specifically for microfluidics, Metafluidics (www.metafluidics.org), which is accessible to both technical experts and amateur makers alike.

Makerspace Community

While general users will be enabled to make microfluidic devices with laser/plotter cutters and 3D printers, adding biological context such as POC testing, sample preparation, and post-analysis quantification may turn the user back to the biological laboratory for further development. The key benefit of the makerspace over having maker-manufacturing capabilities in the biology laboratory is the varied expertise present in the makerspace community. Rather than training biologists in machining, CAD software, and general design rules, these skills can be borrowed through interaction with the makerspace community, which brings a wide array of human capital in forms such as mechanical, material, and electrical engineers, as well as product designers and entrepreneurs. The combined breadth of capabilities and knowledge provided by makerspaces will enable greater potential application solutions than a standalone laser or plotter cutter in a biology laboratory. Bridging a biological application to the materials and tools provided by a makerspace can also be facilitated through this community resource.

Box 2. Design–Cut–Assemble Considerations

Design Considerations	
Gas permeability	While some plastic and adhesive materials such as polymethylpentene are gas permeable, most materials are not and may require venting ports
Inputs/outputs	Connecting tubing to plastic microfluidics can prove challenging; consider a 3D printed connector, using ring magnets as gravity fed wells, or a PDMS block on top
Channel volume	Designing microfluidic channels based on volume enables simpler protocols
Fiducial marks	The addition of fiducial or registration marks play a vital role downstream in alignment for device assembly, imaging, and automation. Consideration should be made as to locations, accessibility, and orientation of fiducial markings at an early stage.
Fluidic considerations	Consider the path of fluids through your device, for example sharp corners and rapid expansions can often hinder fluidic movement and lead to bubbles; also, gas permeable devices may lose fluid due to evaporation.
Cut Considerations	
CAD software selection	Most CAD software can produce acceptable file formats for cutters (*.dxf, *.dwg), oftentimes cutters are directly compatible to select CAD software
Cutting lines	Ensure that no lines are repeated in the drawing to prevent redundant cuts
Cutting resolution	Best resolution can be achieved by keeping the material as flat as possible when cutting; use painter's tape on edges of thin substrates to prevent blowing away on laser cutters or an adhesive backing to prevent unwanted skewing and bowing on plotter cutters
Cutting force	Trial-and-error of laser power/speed and plotter knife force/speed/cut-style is important to get the best cut; an ideal cut for double-sided adhesive would only cut through the first liner and adhesive layer while keeping the bottom liner intact (which will prevent feature 'droop' during the assembly process)
Design vs. cutting	While a design may look perfect on CAD, the order of cuts may cause a feature to blow away or skew during cutting; consider redundant or incomplete cuts that can be manually completed afterwards to overcome these issues.
Assemble Considerations	
Cleanliness	Dust removal is important for microfluidics, a simple cleaning protocol is using a mild detergent and a sonic toothbrush to directly clean plastic surfaces, followed by a wash and dry with pressurized gas or a microfiber cloth; be wary of harsh organics, which may damage substrates.
Feature removal	Use tweezers to remove all unwanted features cut out from adhesive before assembly; it is best to only remove the top liner and adhesive to prevent feature droop during assembly.
Peeling off first liner	Peeling off the top liner from cut adhesive is best done in one continuous motion if possible; tweezers are useful in complicated areas
Alignment	Using a simple alignment rig (such as a dowel for disc devices) is recommended for aligning adhesive on substrates
Lamination	A laminator or even a smooth laminating roller (McMaster–Carr #7533A12) to apply heavy pressure is important to activate most adhesives to set devices together.
Adhesive–paper integration	When a paper substrate is integrated into a thin-film adhesive layer, apply additional lamination pressure at the boundary between adhesive and paper to best seal the device.

Accessibility and Scalability of Microfluidics

Along with enabling integrated microfluidic system development, maker microfluidics addresses another key limitation in microfluidics: accessibility. The use of simple materials and tools to fabricate microfluidic devices obviates the need for clean room facilities and specialized training in photolithographic and soft lithographic methods. Additionally, the application of makerspace principles further allows non-experts in microfluidics to participate. Lesson plans have been developed for students as young as 12 years old to engage in microfluidics, which can be expanded through further makerspace involvement [53,54]. In contrast to clean room facilities, makerspaces grant low-cost access to capital-intensive

manufacturing tools, span a diverse community of individuals from varying backgrounds spanning technical and even nontechnical fields, and promote product development through collaboration and innovation [28]. In addition, the cost of makerspace memberships are comparable to monthly gym memberships at $40–75 per month, while monthly clean room memberships can cost an academic around $1500–3500 and a nonacademic almost $10 000 per month. Material costs are also considerably different, as soft lithography methods use silicon wafer masters ($6–20 each, University Wafer), UV masks ($84 mylar mask, Fine Line Imaging), and polymer ($92/kg PDMS kit, Krayden); whereas makerspaces use low-cost plastics [$5/sq ft (or $13/kg) cast 1/16" acrylic, McMaster–Carr] and adhesives ($2/sq ft Double Lintered Adhesive Tape, Amazon.com). The drastic difference in accessibility is underscored in Figure 3, which shows a technician at work in a clean room in contrast to a high school group learning in a makerspace.

Another key limitation addressed by maker microfluidics is the poor scalability of research-developed platforms to develop into commercial products. In addition to the greater compatibility of makerspace materials with large-scale manufacturing methods, makerspaces allow more seamless device integration with upstream and downstream processing. For example, on-chip sample preparation, sample analysis, and optical detection methods can be designed synonymously in the same space for a potentially instrument-free, sample-to-result microfluidic system. These advantages come with the loss of the superior feature resolution granted by photolithography methods used in clean rooms (hundreds of nanometers) compared to laser and plotter cutters (tens to hundreds of micrometers). However, innovative new microfluidic methods, such as inertial and centrifugal microfluidics, have allowed some users to bypass the need for small features, which may be typically required in applications such as cell separations [55,56]. These methods leverage various inherent physical properties of fluids and particles such as density and size to perform a wide variety of microscale fluid manipulations and processing typically not possible in classic convective flow.

Beyond the scalable prototyping technologies makerspaces offer, one of the most enabling aspects offered by makerspaces is their community-driven nature, which often rivals professional consultants [57]. The creative diversity present in makerspaces allows technical experts

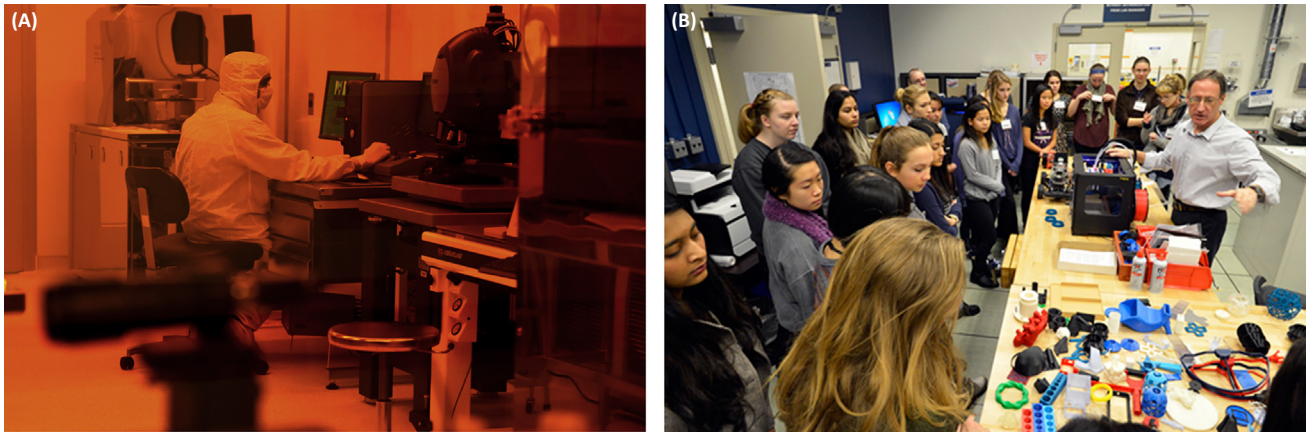

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Figure 3. Contrasting Clean Rooms and Makerspaces. (A) A technician working in the George J. Kostas Nanoscale Technology and Manufacturing Research Center at Northeastern University. Photograph taken from outside the clean room where an orange glass window prevents particular light wavelengths from polymerizing materials inside (Reprinted with permission courtesy of Matthew Modoono and Northeastern University, Boston, Massachusetts). (B) The Technology Office Innovation Laboratory (TOIL) at MIT-Lincoln Laboratory, as an instructor teaches a group of high schoolers how to 3D-print prosthetic hands (Reprinted with permission courtesy of MIT Lincoln Laboratory, Lexington, MA, USA).

in other fields (e.g., computer or electrical engineering) to more easily lend their expertise to microfluidic making in more innovative ways [58]. Maker communities can also help vet community designs (and share with others) for greater focus on reproducibility and efficacy. The big-picture view of makerspace projects will help transition the all-too-often microfluidic 'one-offs' that are only used by the instrument builder to a more standardized and vetted format available to much larger communities.

Concluding Remarks

The benefits afforded by makerspaces, specifically increased participation and the use of low-cost materials and prototyping methods, overcome major barriers to microfluidic device commercialization–accessibility and scalability. While clean room manufacturing may still provide powerful research-scale solutions to massively multiplexed testing and screening (e.g., drug screening, sepsis diagnostics, and ultra-rare cell types), new innovations in microfluidics have obviated some of the need for the ultra-fine resolution of photolithographic techniques for many clinical applications (see Outstanding Questions). Makerspace prototyping promises to increase the success of microfluidics broadly by providing a thriving innovation space for a diverse population to create simple and robust POC microfluidic solutions for current clinical problems.

Outstanding Questions

Can high-resolution features be fabricated in makerspaces in a high-throughput manner?

Can the clean room be moved into makerspaces – similar to the SoftLitho-Box by BlackHoleLab?

Will pipelines be produced to enable microfluidic product development in makerspaces for inventors to rapidly reach the market?

Will manufacturing standards be developed to easily translate devices between different spaces?

How will the advancement of 3D printing materials and techniques influence the development of microfluidic devices?

What novel materials, such as TPX breathable plastic, can be applied to maker microfluidics?

As makerspaces further penetrate into academic instructions, can maker microfluidic training become a standard for future bioengineers?

World-to-chip interfaces: how rapidly will the integration of standard parts (e.g., connectors) occur with the simpler fabrication techniques described herein?

Acknowledgments

The authors disclose receipt of the following financial support for the research, authorship, and/or publication of this article. This material is based upon work supported by the National Science Foundation Graduate Research Fellowship awarded to D.I.W. under grant NSF/DGE-0946746. Research reported in this publication was also supported by the National Cancer Institute of the National Institutes of Health under award number R01CA173712, the National Institute of General Medical Sciences of the National Institutes of Health grant P50 GM098792 and the National Science Foundation's Expeditions in Computing Program under grants 1522074, 1521925, and 1521759. Distribution statement: approved for public release; distribution unlimited. This material is based upon work supported by MIT under Air Force Contract No. FA8721-05-C-0002 and/or FA8702-15-D-0001. Any opinions, findings, conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of MIT.

Appendix A Supplemental Information

Supplemental information associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tibtech.2017.01.001.

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