Review of Low-Cost 3D Bioprinters: State of the Market and Observed Future Trends

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Abstract
Three-dimensional (3D) bioprinting has become mainstream for precise and repeatable high-throughput fabrication of complex cell cultures and tissue constructs in drug testing and regenerative medicine, food products, dental and medical implants, biosensors, and so forth. Due to this tremendous growth in demand, an overwhelming amount of hardware manufacturers have recently flooded the market with different types of low-cost bioprinter models—a price segment that is most affordable to typical-sized laboratories. These machines range in sophistication, type of the underlying printing technology, and possible add-ons/features, which makes the selection process rather daunting (especially for a nonexpert customer). Yet, the review articles available in the literature mostly focus on the technical aspects of the printer technologies under development, as opposed to explaining the differences in what is already on the market. In contrast, this paper provides a snapshot of the fast-evolving low-cost bioprinter niche, as well as reputation profiles (relevant to delivery time, part quality, adherence to specifications, warranty, maintenance, etc.) of the companies selling these machines. Specifically, models spanning three dominant technologies—microextrusion, droplet-based/inkjet, and light-based/crosslinking—are reviewed. Additionally, representative examples of high-end competitors (including up-and-coming microfluidics-based bioprinters) are discussed to highlight their major differences and advantages relative to the low-cost models. Finally, forecasts are made based on the trends observed during this survey, as to the anticipated trickling down of the high-end technologies to the low-cost printers. Overall, this paper provides insight for guiding buyers on a limited budget toward making informed purchasing decisions in this fast-paced market.

Keywords
bioprinting, low cost, extrusion, droplet, inkjet, crosslinking, microfluidics, market, trends

Introduction
Three-dimensional (3D) bioprinting is the process of fabricating anatomically correct tissue constructs via computer-guided deposition of cells embedded in biomaterials (collectively known as “bio-ink”) to specific locations. Due to its potential for high-throughput biomanufacturing of complex organs and tissues with both precision and accuracy, the technology has been quickly emerging as a major competitor to conventional tissue engineering methodologies.¹-⁴ In fact, the global market share for 3D bioprinting is expected to break into the ~$1.5 billion (USD) range in the mid-2020s, almost 30% of which is attributed to North America.⁵-⁷ With such explosive growth, all of the 3D bioprinting sectors are expected to witness a high volume of expansion, especially in medical and dental areas (Fig. 1). Additionally, the global 3D food printing market should grow from $485.5 million in 2020 to $1 billion by 2025, at a compound annual growth rate (CAGR) of 16.1%.⁸ Consequently, there is also an increasing demand for...
bioprinting equipment in both industry and academia. Yet, the cost has been prohibitive for most small and medium laboratories and medical practices; for example, some of the current professional, automated, high-end bioprinters can cost upward of $1 million.

Recently, however, a wave of new start-up companies has begun to introduce low-cost bioprinting solutions to the market. Due to their affordability, these systems hold a tremendous potential for the development of regenerative medicine technologies. Yet, due to the novelty of this niche market, no bioprinter reviews that we could find focus on the latest commercially available low-cost systems. Specifically, the previously published reviews either give an overview of the entire bioprinting field (with a focus on the evolution of the printing technologies),\textsuperscript{9–13} review bioinks,\textsuperscript{14–27} or discuss specific applications (e.g., cardiovascular tissue models,\textsuperscript{14,28–35} bone tissue models,\textsuperscript{36–48} cartilage tissue models,\textsuperscript{42,47,49–52} nerve tissue models,\textsuperscript{53–61} skin tissue models,\textsuperscript{48,62–66} and in vivo bioprinting\textsuperscript{67–69}). We have found only one review that discusses the commercially available machines and profiles their manufacturers.\textsuperscript{70} However, this publication is already 3 years old. Many new companies and 3D printer models have been introduced to the market since 2018. Furthermore, none of the above reviews focus on the low-cost systems, which is now an emerging 3D bioprinter market.

Consequently, due to the fast-paced evolution of these technologies, combined with the lack of an established reputation by the companies (many of which are start-ups) developing them, it may be challenging for an inexperienced customer to make an informed purchasing decision. This is significantly exacerbated by the fact that many systems claim to have similar printing resolutions and other specs. Therefore, for these reasons, the key goals of the paper over previous reviews are to (1) provide the latest snapshot of the technologies and machine models currently available in the low-cost 3D bioprinter market segment; (2) profile the scholarly impact, market presence, and maturity of the companies that manufacture the low-cost printers, in order to help an inexperienced buyer mitigate the risks (e.g., delayed delivery time, poor part quality, lack of technical support, and unstable warranty) associated with their potential investment; (3) compare and contrast the technical features between the low-cost and high-end printers, in order to help the reader to understand the main differences between what the models can offer them; and, finally, (4) highlight the emerging technologies used by the high-end printer space, in order to forecast their trickling down to the low-cost machines in the near future.

To that end, the organization of this paper is as follows: First, we provide a brief snapshot of the 3D bioprinter market, which shows how the technologies vary based on cost among all (i.e., both low-cost and high-end) of the models currently available for purchase. Then, we give a detailed overview of the low-cost 3D bioprinter market segment, which we cluster by the three predominant technologies used in these machines: microextrusion, droplet-based and light-based. This is followed by a brief overview of the high-end 3D bioprinter market, where we summarize the main advantages of these pricier machines over their cheaper counterparts. Additionally, this section introduces the emerging microfluidic print head technology. Finally, the paper is concluded with projections of how the low-cost 3D bioprinter market will evolve in the near future, based on the expected trickling down of the technologies currently used in the high-end machines.
In order to define what a low-cost bioprinter is, we first looked at the price distribution of the currently available commercial models and binned them into two halves (Fig. 2). Based on our personal experience, the price that corresponds to this boundary also happens to be around the rough upper limit of what is considered to be affordable by most small companies and laboratories. Therefore, we classify the printers below this threshold to be a “low-cost,” while the ones above it we consider to be “high-end.”

Furthermore, it can be seen from Figure 2 that North America, Europe, and East Asia are currently the main leaders in providing 3D bioprinters. Interestingly, our market search also showed that most of the recently released models belong to the low-cost category: for example, BIO X, Allevi 1, Allevi 3, BIOBOT BASIC, Lulzbot Bio, Lumen X, Felix BIOprinter, STEMaker, REG4LIFE, and AXO A1-A6. This suggests that the bioprinter space is undergoing a dynamic shift toward low-cost solutions and that, over time, the increasing availability of such machines will change the landscape of the 3D bioprinting market.
The technological differences between the printer models can be largely attributed to the product specifications desired by the end user. For example, the major machine attributes that should be considered when making a purchasing decision include the underlying printing technology (broadly classified into microextrusion-based, droplet-based/inkjet, and light-based crosslinking), positional accuracy, build volume, print bed and/or print head temperature control, material compatibility, calibration automation, and customizability. Furthermore, the printing method is essential for the efficacy of the bio-ink because the cells within it have to survive and remain undamaged through the printing process to remain viable postfabrication. Although the high-end models excel at most of the above characteristics, the low-cost bioprinters are beginning to offer many of the similar (at least on paper) features as their more expensive competitors. Yet, the price disparities remain and can be as large as two orders of magnitude; therefore, it is important to understand the differences between the bioprinters in the two price brackets, as well as the main trade-offs characteristic of each respective market segment. To that end, the section entitled “A Detailed Overview of the Low-Cost 3D Bioprinters” overviews what is currently available in the low-cost bioprinter space, while the section entitled “A Brief Overview of the High-End 3D Bioprinters” contrasts these machines to their established high-end competition in the upper price bracket.

A Detailed Overview of the Low-Cost 3D Bioprinters

Although there are many excellent general reviews of the available bioprinter technologies, here, we focus on highlighting and comparing some of the low-cost models’ key features. A critical difference between them that is most immediately apparent to the eye is that some of the printers adopt an open-frame style, while others have a closed frame. The trade-offs between them are that the former allows easier access for observation, interaction (e.g., experiment customization), and printer head maintenance, while the latter is meant to mimic the sterile environment of a biohood via a built-in sterile chamber, with high-efficiency particulate air (HEPA) filters, a UV-C lamp (e.g., 254, 265, or 275 nm) for disinfection, and transparent windows for observation. Although the open-frame printers are typically small enough to be placed inside of a biohood, the vibrations caused by its large air pump can be disruptive to a high-resolution printing process. Therefore, the onboard sterility chamber of the closed-frame printers is typically designed to have lower vibrations when compared with those of a conventional biohood. Additionally, a sterilizing UV lamp is sometimes added to the closed-frame models by the manufacturer. Finally, another peripheral consideration is that some of the platform configurations are integrated with a liquid crystal display (LCD) and USB port, which allow these printers to work independently from a computer. This can be an important consideration in case it is not practical to maintain a physical connection with the printer when placing it inside of a biosafety cabinet (BSC), given the wire may obstruct its hood from closing.

Furthermore, the low-cost bioprinters are commonly equipped with light-emitting diodes (LEDs), which enable the crosslinking of the bio-ink materials (e.g., a hydrogel mixed with a photoinitiator) upon the extrusion. Popular light sources used in this process are ultraviolet (UV) 365...
nm and blue 405 nm wavelengths. Temperature control is also typically included via a heating or a cooling jacket around the syringe. This can be useful for maintaining physiological culturing conditions, for cell preservation via cooling, and/or for changing the viscosity of the bio-ink. Moreover, some models come with a cooled/heated print bed (also to help maintain the 37 °C body-like temperature and/or switching between solid/liquid stages of the thermosensitive biomaterials), which is sometimes shaped, or include the adapters for standard-sized petri dishes, well plates, and microscopy slides.

Finally, some printers are equipped with a filament extruder, which allows the printers to print melted thermoplastic (cell-free) filament. This is especially useful for the fabrication of scaffold support for cell-laden tissues by enabling the deposition of the “scaffolding” thermoplastic materials in tandem with the cell-laden “bio-ink.” Optionally, inspection cameras are also included in order to provide the user with a zoomed-in observation of the printing process. An overall summary of the low-cost bioprinters’ technical features and attributes is presented in Supplemental Table S1.

A common pattern that can be observed from Supplemental Table S1 is that all of the low-cost bioprinters use microextrusion (as opposed to the droplet-based or laser-assisted methods) as the printing technology. Most of them (~85%) are equipped with print head and/or print bed temperature control, and about three-quarters have light-based crosslinking options. The closed-frame architecture is slightly more (~55%) common than the open one. Among the 3D bioprinters with closed-frame architecture, more than 73% are equipped with sterilization or customization for additional costs. Furthermore, most of them come with multiple print heads for multimaterial prints (~70%); a print bed temperature control option (~85%); a print head temperature control option (85%); various print bed auto-calibrations (77%); an inspection camera (59%); and onboard display options (~70%). Finally, we chose not to report the printing resolution because it depends on multiple parameters, such as the accuracy and precision of the XYZ motion (typically anisotropic), the nozzle gauge and dispensing resolution, and the ink’s material properties at the printing conditions (typically unique to the experiment). For that reason, it is difficult to define, and as a result, the companies either do not report the resolution at all or quote a misleading “theoretical” resolution that is difficult to achieve in a real setting. Therefore, we will simply state that for extrusion-based methods, the best attainable feature size for a nonexpert user is around 200 microns.76

**Microextrusion-Based Bioprinting Technology**

Microextrusion-based 3D bioprinting technology is beneficial for the rapid fabrication of large (>1 cm³) and complex cell-laden/cell-free structures composed of more than one material or cell spheroids.77 This technology works with a wide range of materials with a viscosity of ~30 mPa/s to >6 × 10⁷ mPa/s and has the advantage of precise deposition/controllable cell distribution.78 The microextrusion-based 3D bioprinting is usually clustered into two main categories: mechanical and pneumatic extrusion, as illustrated in Figure 3. In mechanical extrusion, the process is typically driven by a stepper motor, which turns a threaded screw (Fig. 3a). The screw serves as an output shaft for translating the rotating motion into the linear actuation of a plunger. The plunger then generates a compression force on the piston of a syringe, which contains the bio-ink. The rotation of the stepper motor defines the speed and quantity of the extrusion, thereby allowing the printing process to be controlled by a computer program. Meanwhile, the gauge of the syringe’s needle acts as a nozzle and defines the diameter of the extruded filament. It is also noteworthy to mention that there is a variant of mechanical extrusion that uses a turning screw (not shown), like what is used in industrial screw-driven polymer extruders, to push the bio-ink out of the nozzle. However, this method is less popular because it can introduce unjustified damage to the cells inside of the bio-ink.78

Pneumatic extrusion, on the other hand, is actuated by means of compressed air (or another gas, e.g., a blend of air and CO₂ for the culture pH control), which is pushed through by a pump (Fig. 3b). Like the mechanical extrusion, the compressed gas displaces the bio-ink inside of a syringe in order to inject it through the needle. The pneumatic extrusion can be automatically controlled using a programmable pressure controller. And as can be seen in Figure 3, the printer head is more compact compared with the mechanical extruder; however, it requires an external pump, which may result in an additional expense to the customer. An advantage of pneumatic extrusion over the mechanical type is that it is contact-free, which can translate into greater sterility and less cell damage. Therefore, it usually replaces the mechanical extrusion on the more expensive versions of the low-cost bioprinters.

**Low-Cost Microextrusion-Based Bioprinters**

Supplemental Figure S4 shows photographs of all low-cost microextrusion-based 3D bioprinters listed in Supplemental Table S1.

**3D Cultures’s Tissue Scribe.** According to our market search, Tissue Scribe is the most economical and compact single-nozzle 3D bioprinter on the market. It was first released in 2017 by an American-based start-up company with around 10 employees (3D Cultures). The Tissue Scribe is a single-nozzle mechanical extrusion-based printing system with a starting price of ~$1500 (publicly available online) and no
additional cost for the control software. Each Tissue Scribe unit is equipped with one extruder, which has a housing slot for a fixed syringe volume. There are three modular print heads available to be selected: a mechanical extruder with a housing slot for a 1 cc syringe, 3 cc syringe, or 10 cc syringe. Furthermore, all three modular print heads can be purchased separately for an extra cost of $750 each. Additionally, the bioprinter system can be converted to a conventional polymer melt 3D printer by replacing the mechanical extrusion head with a pellet extrusion tool for an additional cost of $1000.

The Tissue Scribe’s XYZ position accuracy is 100 × 100 × 44 µm. Therefore, the 3D bioprinter is suitable for any starter and research lab without the need for a major financial investment. The Tissue Scribe is integrated with an LCD display, interactive control knob, and panel for easy adjustments and calibration. The advantage of this system is that it has temperature control for both the print bed (up to 60 °C) and the printing head (up to 70 °C), which can be tuned to a physiological temperature at ~37 °C to work with temperature-dependent hydrogel/materials or sample with cells. With a small footprint of 29 × 19 cm², the Tissue Scribe is able to fit in most BSCs for sterile printing. It can print directly from .gcode file on a microSD card (which does not require a continuous connection to your computer). Gcode files can be generated from the open-source software (e.g., Cura or Repetier-Host) and downloaded to the microSD card for subsequent loading onto the printer.

The Tissue Scribe has been used for various applications in tissue engineering, dental, and materials testing/optimization research, such as is used in biofabricating 3D tumor models, cell-laden hydrogels for cell–cell interaction study, nanocomposite hydrogels for cell migration study, gelatin hydrogel properties and 3D bioprinting process optimization, highly elastomeric and property-tailorable hydrogels, 3D printed smart dental implants, biomaterials and 3D/4D printed thermosensitive and photoactivated smart materials, and 3D printed porous structures with shape memory properties.

**Advanced Solutions Inc.’s BIOBOT BASIC.** BIOBOT BASIC is the world’s first polar coordinate bioprinter, introduced in 2019 by an American company, Advanced Solutions Inc. The company offers both high-end (BioAssemblyBot) and low-cost (BIOBOT BASIC) 3D bioprinter systems in its product catalogs. At a starting price of ~$5000 (publicly available online), the BIOBOT BASIC is a versatile benchtop 3D bioprinter that comes with a patented unique revolver-inspired pneumatic extrusion head with a working pressure range of 0.5–85 psi. This tool can print up to five different biomaterials without the need to disrupt the extrusion process by manually switching bio-ink cartridges. Instead, the turret has a turbine-like drum with five mounting slots for 10 cc syringes, which are automatically rotated in and out of the dispensing position during the printing process. The positional repeatability and resolution of the BIOBOT BASIC is 10 µm in both the rotary and Z directions.

Furthermore, unlike the other machines on the market, whose printer heads follow linear XYZ motion on a stationary print bed, the BIOBOT BASIC’s extruder tool is constrained to the Z direction. In contrast, its bed moves in the radial and rotary fashion during the printing process, which provides a relatively large print space while maintaining an overall small footprint on the platform. With a maximum print size of diameter 19 × 10 cm (which corresponds to a maximum build volume of 1134 cm³ within the print area), the system can deposit the designed structure directly on glass slides, petri dishes, or multwell plates. Moreover, the system utilizes a laser-based calibration system mounted on one side of the print bed, which can automatically scan and take XY positional measurements of the nozzle and calibrate itself for different materials and needle sizes. It is not restricted to the nozzle length and gauge; however, ¼- or ½-inch-long needles are recommended by the manufacturer.

Even though the BIOBOT BASIC does not have temperature control for either the extrusion system or the print bed, it is considered to be an excellent entry-level, low-cost 3D bioprinter system that can fit most BSCs/fume hoods. Moreover, it can be operated and monitored by Advanced Solutions’ Tissue Structure Information Modeling (TSIM) software. TSIM allows the user to either create 3D computer drawings of the desired tissue structure from scratch or import them from magnetic resonance imaging (MRI) or computed tomography (CT) scans. The images can then be freely manipulated to add or remove components or assign material properties to different geometry sections. The BIOBOT BASIC’s purchase includes a 1-year TSIM software trial, followed by an annual subscription. The machine has been recently used for 3D printing and characterization of human nasoseptal chondrocyte-laden, dual-crosslinked, oxidized alginate–gelatin hydrogels for cartilage repair approaches.

**Hyrel 3D’s Engine SR and Engine HR.** The Engine SR and HR are highly affordable and compact 3D bioprinters produced by Hyrel 3D Inc., a small US-based company founded in 2012 with around 100 employees in four countries. The company has seen much popularity in both the bio and non-bio printing research fields, with more than 216 publications and documents using the Hyrel machines, according to their website (as of December 2020). Their major applications include bone tissue engineering and electronics. The Engine SR is one of the most affordable bioprinters on the market, with only ~$2500 as its price tag (publicly available online). In comparison, the Engine HR is a more compact, more expensive version (~$8000) of the SR model. Both the Engine SR and HR are equipped with
an integrated camera and a touch screen Windows 10 tablet personal computer (PC), with all the software included in the purchase price. In addition, compared with other printers on the market, the Engine SR offers a very large build volume of up to 20 × 20 × 20 cm³ (Suppl. Table S1). For the price difference, the Engine HR offers superior XYZ positional accuracy (12 × 12 × 10 µm) and repeatability (12 × 12 × 5 µm) compared with the Engine SR’s position accuracy of 50 × 50 × 10 µm and repeatability of 25 × 25 × 5 µm. For this reason, the Engine HR is very promising for the printing of tissues at high accuracy.

The major selling point of the Hyrel 3D’s machines is the high level of customization that they possess. For example, customers can select modular print heads of interest from a wide range of options, such as syringe-based extrusion, filament extrusion, and photo-crosslinking heads. Hyrel 3D offers the widest variety of modular print heads from any other company that we have surveyed for this paper. Additionally, the company develops on-demand custom-built print heads. One such example is their “on-the-fly” microfluidic mixing, extrusion, and UV crosslinking one that were developed for the fabrication of heterogeneous tissue scaffolds in collaboration with Professor Hala Zreiqat’s group from the University of Sydney.96

Among the assortment of Hyrel 3D’s modular printer heads, the Syringe Dispensing System (SDS) is the most relevant to bioprinting. However, a Crosslinking Dispensing System (CDS) modular head is also available at different wavelengths, such as 280, 310, 365, 405, and 450 nm. The SDS heads cost $400, while the CDS heads cost $550; both are made for single 5, 10, 30, or 60 cc syringes. Moreover, the 1:1 dual 25 cc syringe head or the programmed ratio dual heads are capable of printing up to two different materials simultaneously and can be purchased for $500. Other modular heads enable the operator to create more intricate fabrications using nonstandard scaffold materials, by drilling the scaffold or etching it using a laser.97 This range of modular heads makes the Engine SR and Engine HR machines a lot more versatile than just a conventional bioprinter.

Finally, it is noteworthy to mention that Hyrel 3D has two other models, which are compatible with all of their print heads (including those capable of printing bio-ink): the Hydra 16A and the System 30M. However, these models are too large to fit into a standard BSC, and they are not equipped with a sterile printing environment. Therefore, we did not review these models.

**Lulzbot’s 3D Bioprinter.** Lulzbot Bio is the first open-source Fluid Deposition Fabrication 3D bioprinter that is manufactured by Aleph Objects. Founded in 2011, Aleph Objects is a reputable 3D printer manufacturer that has been on the market for the past decade. The machine is available for purchase at ~$10,000 (publicly available online), making it one of the most affordable on the market. This model has a small footprint (46 × 41 cm²); therefore, it can fit in most BSCs. Lulzbot Bio’s maximum build volume is 16 × 16 × 8.9 cm³, and its XYZ position accuracy is 10 × 10 × 5 µm. The bioprinter system is equipped with one mechanical extruder without temperature control, an SD card slot for easy operation without the need to be tethered to a computer, a user-friendly interactive LCD touch screen for print bed temperature control and calibrations, and preconfigured material profiles in Cura LulzBot open-source software. Moreover, its freely licensed designs and specifications allow modifications and improvements to both the software and hardware. All of the machine’s parts/components are freely available for purchase on Lulzbot’s Open Hardware Assembly Instructions website.

Furthermore, for the printer’s creation, Aleph Objects partnered with a 3D printing services company, FluidForm, because of its innovative proprietary FRESH (Freeform Reversible Embedding of Suspended Hydrogels) technology.98–100 The advantage of this process is that it allows for the 3D bioprinting of soft cell-encapsulated materials, such as collagen or alginate. This is achieved by embedding them in a hydrogel (composed of processed gelatin microparticles) that serves as a temporary, thermoreversible support, which is then washed away after the printing. In order to melt the hydrogel, the printing bath is warmed up to ~40 °C, which is well tolerated by the cells. For this reason, the bioprinter system is equipped with a thermoregulated print bed and is capable of printing soft materials with an elastic modulus <500 kPa.98

**Allevi’s 1, 2, and 3.** Allevi, formerly known as BioBots, is a company with around 12–15 employees founded in 2014 in Philadelphia, Pennsylvania, out of the University of Pennsylvania.101 Allevi is currently offering three versatile, accessible desktop 3D bioprinters: Allevi 1, Allevi 2, and Allevi 3. All three models fall into the low-cost bioprinter market segment, with no additional costs required for the company’s Bioprint Essential software. The product’s name, Allevi 1, 2, or 3, represents the number of autocalibrated pneumatic microextruders that are equipped with each model: one, two, and three, respectively. All the Allevi models fit into a space of 1 ft³, allowing them to operate in any BSCs.

The Allevi 2 is the most economical bioprinter from the series. It provides a 7.5 × 7.5 × 5 µm XYZ precision accuracy and is equipped with visible light photocuring at 405 nm and heated pneumatic extruders (RT through 70/160 °C) (Suppl. Table S1). The Allevi 2 (BioBot 1 originally) has been used in various research projects, for example, testing the quality of cell-laden hydrogel-based bio-inks;102–104 investigating the effects of the extrusion process on printed constructs;105,106 printing polydimethylsiloxane (PDMS) devices;107 and generating a sacrificial scaffold for a
thrombosis-on-a-chip. It is also further highlighted in many other peer-reviewed publications.

Alternatively, the Allevi 1 and 3 offer better XYZ precision accuracy: 5 × 5 × 5 μm and 1 × 1 × 1 μm, respectively. Also, the Allevi 1 and 3 are equipped with cooled/heated pneumatic extruders, which can regulate the printing material’s temperature from 4 to 160 °C. Therefore, it is compatible with a wide variety of hydrogels, from collagen to poly(lactic-co-glycolic acid) (PLGA). Among the three Allevi bioprinters, the Allevi 3 is the only model with a thermoregulated print bed (RT through 60 °C) and a pneumatic pump with printers, the Allevi 3 is the only model with a thermoregulated

tic-co-glycolic acid) (PLGA). Among the three Allevi bio-

process on different surfaces: in a well-plate, in a petri dish, and so on. In terms of applications, the printer has been used in basic scientific research such as cartilage tissue engineering and has been cited in several peer-reviewed articles. It has also been sold in more than 25 countries.

**ROKIT HEALTHCARE’s DR. INVIVO 4D2.** DR. INVIVO 4D2 is a tabletop affordable model introduced by ROKIT HEALTHCARE Inc., a bioprinting and biotechnology company based in South Korea. The company originally built its reputation as a manufacturer of nonbio 3D printers. However, after having received a $3 million government grant to co-develop an in situ 3D bioprinting system for skin regeneration in 2015, ROKIT HEALTHCARE launched its first ROKIT INVIVO Bioprinter model in 2016. Currently, it offers three DR. INVIVO 4D2 versions at different price points: a standard version, an upgrade version, and a premium version. When compared with the other bioprinters on the market, DR. INVIVO 4D2 offers several benefits, such as being in an enclosed sterile chamber with an H14 HEPA filter, a 253 nm disinfection UV lamp, a large XYZ build volume (10 × 10 × 8 cm³), high XYZ movement precision (1 × 1 × 10 µm), automated calibrations, and free specialized software (Suppl. Table S1). Another advantage of the unit is that it has an integrated LCD touch display, making a computer connection unnecessary. In fact, the printing can even be done via Wi-Fi from an Android phone.

Both the standard and the upgrade versions are equipped with one mechanical syringe extruder and one thermoplastic extruder (up to 250 °C), making it suitable for scaffold-based and cell-laden tissue fabrication. The premium version is equipped with three different extruders: a mechanical syringe extruder, filament extruder (up to 250 °C), and hot-melt pneumatic extruder (up to 350 °C and 900 kPa maximum operating pressure). The standard version does not have a mechanical print head, photocuring, or temperature control for the print bed. However, for the higher price points of the upgrade and premium versions, a UV LED 365 nm (405 nm optional) for photo-crosslinking and an inspection camera with a Wi-Fi connection are integrated into each unit. Additionally, a digital thermometer is also integrated into the premium version.

As shown in Supplemental Table S1, DR. INVIVO 4D2 (upgrade/premium version) is currently the only bioprinter on the market that has a print bed and mechanical extruder temperature control system in which the printing environment can be regulated to as low as −4 °C (for higher spatial resolution and tolerance) and heat up to 60 °C. Finally, ROKIT HEALTHCARE’s DR. INVIVO system has become an immensely popular tool that was cited in more than 60 publications (see Fig. 6) in a variety of applications, such as additive manufacturing for tissue engineering and regenerative medicine, drug testing, and pharmaceutical and biomaterials research.
addition to the low-cost DR. INVIVO 4D2 series, ROKIT HEALTHCARE just released a new high-cost model in 2020, INVIVO 4D6 HEALTHCARE (Suppl. Table S2).

Axolotl Biosystems’ AXO A1, AXO A2, AXO A3, and AXO A6. Axolotl Biosystems is a privately held Turkish company founded in 2016 with about 10 employees. In 2020, they released three fully customizable and affordable desktop 3D bioprinters: AXO A1, AXO A2, AXO A3, and AXO A6. A bio-ink starter kit, a UV curing kit, and a scaffold starter kit are also included in any 3D bioprinter purchase.

Despite the price gaps, all three models are designed to achieve a high-precision XYZ movement of ~1.25 µm and have a modular structure for interchangeable print heads. According to our market search, the AXO A1 is currently one of the top 5 most affordable 3D bioprinters on the market. The machine is equipped with sockets for interchangeable print heads. The basic unit includes a pneumatic print head (RT through 210 °C), heated print bed (RT through 60 °C), UV crosslinking tool head, air compressor for a working pressure range of ~14–145 psi, individual digital temperature indicator for each of the print heads, nozzle autocalibration, and free control software that works with .stl and .gcode files. Even though the AXO A1’s chamber is not enclosed, it is a very compact bioprinter with a dimension of 34 × 34 × 35 cm³. This means that it can fit into most BSCs for a sterile working condition when handling the bio-ink with cells. The AXO A2 shares the same basic configuration as the AXO A1; however, it has been upgraded to work with two different print heads to deposit multiple materials interchangeably. At the higher price tags, the AXO A3 has three available sockets for the modular tool heads, and the AXO A6 has six available sockets for the modular tool heads. The machine comes with a heated print head (RT through 210 °C), extra heated print head (30–265 °C), cooled print head (3–65 °C), 405 nm UV curing tool head, high-definition (HD) camera tool head, and cooled/heated temperature-controlled print bed (5–60 °C). The AXO A2, AXO A3, and AXO A6 models are stand-alone benchtop 3D bioprinters that are equipped with a HEPA filter that has a 0.2 µm filter membrane and with an enclosed chamber for providing sterile conditions during the bioprinting process (without the need for a BSC).

Axolotl Biosystems also offers a compatible melt electrowriting system for an additional cost and an extra cooled print head, as well as a cooled print bed system. Moreover, additional modular heads are also available for purchase: an extra heated pneumatic print head, a mechanical extrusion print head, a solution electrospinning print head, an HD camera tool head, a 200 mW UV curing tool head 405 nm, a 50 mW UV curing tool head 405 nm, and a 10 mW UV curing tool head 365 nm. Given the novelty of these machines and the newly released 2020 models, there is only a study that used AXO A2 for developing UV curable and bioprintable new bio-ink.

FELIXprinters’ FELIX BIOprinter. Founded in 2011, FELIXprinters is a Netherlands manufacturer with about 10 years of experience developing robust and cost-effective (nonbio) 3D printing solutions. In collaboration with TRAING4CRM and the Technical University of Denmark, FELIXprinters launched its first affordable 3D bioprinter in 2020. The FELIX BIOprinter is a compact model (43 × 39 × 55 cm³ in XYZ dimensions) that can fit under any BSC/fume hood. The machine is utilized with two cooled/heated sterilizable mechanical extrusion print heads with linear motors that can print using two bio-inks interchangeably (7 × 7 × 1 µm XYZ resolution; XYZ positional accuracy can be fine-tuned to ±10 µm); a temperature control print bed; a UV 365 nm LED for photocuring; automatic bed leveling and calibration with nozzle probing; a transparent cover (optional); a 5 MP webcam for monitoring the prints remotely from a smartphone or PC; a user-friendly LCD touch screen with Wi-Fi connection, and open-source software. The mechanical extrusion print heads are compatible with any standard 5 mL syringe and are designed to work with a wide range of materials (with viscosities up to 64,000 mPa/s). The temperature control range for both the print head and the print bed is 0–50 °C, with a variation of 0.5 °C. FELIX BIOprinter is also designed for fitting standardized petri dishes and comes with an adapter for culture plates.

In terms of applications, FELIXprinters’ machines have been used for the development of 3D cell culture scaffolds/systems; precise positioning of a picosecond-pulsed electrode for targeted electrostimulation; manipulation of cell proliferation; and inducing lineage-specific gene expression in neural and mesenchymal stem cells.

Brinter’s Bioprinter. Brinter is a 3D bioprinter manufacturer based in Finland, which is a spin-off from another company called 3DTech Ltd. Brinter released its first versatile benchtop machine in 2020. Brinter 3D’s platform is a revolutionary modular machine offering versatile printing modalities in a single product. The company offers a unique patent-pending modular concept for an easy-to-change dispensing tool, which is a cost-effective way to make future dispensing head application updates without the need to purchase a new printer. As with the other modular print head machines, the concept offers a high degree of customization tailored to the customer’s unique needs. Brinter’s product is affordable, and the prices are clearly disclosed on the company’s website. For example, the base Brinter system cost ~$30,300 (publicly available online). There are currently nine different modular print heads available for purchasing: no temperature control Pneuma tool (~$910); heated Pneuma tool (~$2400), no temperature control Microdroplet tool
joined its Scientific Advisory Board. According to our one of history’s most prolific inventors in medicine—has Langer from the Massachusetts Institute of Technology—in less than 10 months. Most recently, Professor Robert whose business became rapidly successful and went public CELLINK’s INKREDIBLE, INKREDIBLE +, and BIO X. saccharides for casting, injecting, and 3D fabrication. The Brinter has been used in the novel bio-ink, for example, photo-crosslinkable methacrylated polypeptides and polysaccharides for casting, injecting, and 3D fabrication.  

CEILINK’s INKREDIBLE, INKREDIBLE +, and BIO X. CEL- LINK is a Sweden-based company founded in January 2016 whose business became rapidly successful and went public in less than 10 months. Most recently, Professor Robert Langer from the Massachusetts Institute of Technology—one of history’s most prolific inventors in medicine—has joined its Scientific Advisory Board. According to our market search, CELLINK’s first 3D bioprinter model, INKREDIBLE, is one of the most cost-affordable machines currently available on the market. It is equipped with a dual extruder pneumatically driven by an isolated pumping system and has built-in UV crosslinking at 365 nm LED (405 nm is optional, for an additional cost). However, the INKREDIBLE does not have thermal regulation for both its print bed and its extruders. The compact nature of the printer ($33 \times 38 \text{ cm}^2$) makes it preferred by many researchers, especially those with small lab space, as it can fit well in most BSCs.

The more advanced INKREDIBLE+ is an improved version of the INKREDIBLE. It comprises all the important features of the cheaper version but is further upgraded with a sterile chamber and an H13 HEPA filter, allowing the printer to work without the need for a regular BSC. The machine also comes with a built-in UV crosslinking system that uses 365 and 405 nm wavelengths. Furthermore, the dual pneumatic extruders of the INKREDIBLE+ can be heated from RT to 130 °C, thereby making it possible to work with a wide range of thermally sensitive biomaterials and/or to maintain ~37 °C during the printing process in order to maximize the cellular viability. A built-in temperature control print bed option is also available as an add-on for the INKREDIBLE+. Even though its price is roughly double that of the economical version, the INKREDIBLE+ is still considered to be affordable for many laboratories. Expectedly, it was found to have been used in many scientific research publications, some of which target a variety of tissue types, such as cartilage, musculoskeletal, and bone, and use a wide range of biomaterials.

The BIO X is a more recent product from CELLINK. It was released in 2017 and offers several advanced features compared with those of the INKREDIBLE and INKREDIBLE+. For example, the printing resolution is increased four times (XYZ precision accuracy: $2.5 \times 2.5 \times 2.5 \mu\text{m}$) compared with that of its predecessors (XYZ precision accuracy: $10 \times 10 \times 2.5 \mu\text{m}$) (Suppl. Table S1). The BIO X is also equipped with three slots for interchangeable modular print heads, which allows the user to have greater customization over the printing process. For example, among the more conventional options are the following: three heated pneumatic print heads (RT through 65 °C), one thermoplastic print head (RT through 250 °C), one cooled–heated pneumatic print head (4–65 °C), and 365 or 405 nm photocuring modules for general crosslinking. Furthermore, more specialized alternatives are also available for purchase, such as a heated mechanical extrusion print head (RT through 65 °C), electromagnetic droplet print head for inkjet printing, HD camera tool head, and photocuring tool head with wavelengths of 450, 485, and 520 nm, or a custom wavelength per the customer’s requests. The BIO X clean chamber has a large observation window and inspection camera, making it easier to monitor the printing process from different angles. Moreover, the dual H14 HEPA filters and disinfection UV-C Lamp 275 nm were upgraded relative to the INKREDIBLE+, in order to meet higher sterility requirements. The built-in temperature-controlled print bed (4–60 °C) is another improvement relative to the other models.

All CELLINK’s bioprinter models come with an intuitive LCD controller, nozzle length autocalibration, and manual pressure regulators for precise regulation of any dispensing process. Additionally, the BIO X comes with autobed leveling. Finally, the software bundle (including Slic3r, Repetier-Host, and HeartWare) is included at no cost.

**Droplet-Based Bioprinting Technology**

The droplet-based bioprinting systems commercially available today typically use two drop-based technologies. The first is piezoelectric drop-on-demand (PDOD) technology, in which a piezoelectric actuator is used as a droplet generator. The operational mechanism is well known to be a push–pull process, actuated by the deflection of the piezoelectric component attached to the printer’s print head. The deflection generates an acoustic wave across the printed material’s volume, pushing it toward the nozzle. A droplet is then formed outside of the nozzle by surface
tension. Finally, the piezo component is released from the stress, which pulls the bio-ink material back as the droplet is dispensed onto the print substrate. The second is high-speed microsolenoid valve technology for droplet generation, in which droplets are formed through the nozzle through the combination of the syringe pump and the micro-solenoid valve attached to the print head (Fig. 4b).

Compared with the microextrusion methods (see the “Microextrusion-Based Bioprinting Technology” section), the main advantage of droplet-based bioprinting is its ability to fabricate high-resolution constructs, while at the same time maintaining a high cell viability of ~80–95%.18,152 For example, the latter technology was used to fabricate constructs at a very high cell density (tissue-relevant densities of ~10^7 cells/mL) and droplet resolution of 1 nL, while maintaining a cell viability of ~90%.77 This is largely due to the fact that the droplet-based machines use lower-viscosity bio-inks, which impose less shear stress on the cells and provide a higher printing resolution (droplet size as small as ~50 µm), greater accuracy, and faster dispensing speed than the extrusion-based competitors.153,154

Conversely, the microextrusion technologies lack the ability to control droplet size and are thus forced to utilize more viscous bio-inks (squeezed out in the shape of a filament). This necessitates the use of higher dispensing pressure in order to push the material through a small “nozzle,” which in turn leads to significant cell damage due to the elevated shear stresses (>10 kPa) experienced during the passage of the bio-ink through the needle tip’s narrow opening. Consequently, decreases in cell viability and proliferation are experienced with the use of small (e.g., an inner diameter <200 µm) needle sizes,77,155 and as a result, a printing resolution <100 mm is difficult to achieve using microextrusion.153,154

Nonetheless, despite the advantages of being able to maintain both high cell viability and a high resolution simultaneously, the droplet-based printers are also limited in that they can only use lower (3.5–12 mPa/s)-viscosity materials, such as alginate or collagen.18 The use of low viscosity also leads to the difficulty of building supporting frames or structures. This makes it challenging to fabricate tall 3D prints.

Additionally, nozzle clogging is a common problem for droplet-based printing techniques that handle high-cell-density suspensions.156 However, when the needle size is smaller than 150 µm, clogging becomes a major problem for the extrusion-based methods as well.157–159

Low-Cost Droplet-Based Bioprinters

Droplet-based (i.e., inkjet) technologies were first used for cell patterning77,152,160 and ultimately served as the foundation for the early commercial bioprinters back in 2005.4 Their main advantages over microextrusion-based 3D bioprinters (Suppl. Table S1) are a larger build volume, high resolution (as fine as ~1 pL droplet volume or ~20 µm features), and faster printing speeds. Additionally, the inkjet printers provide a high degree of customization via fine-tunable droplet control software and print process monitoring hardware (e.g., cameras for droplet observation) that enable semiautomated calibration and alignment modes. However, the droplet-based printers were always expensive, and while the emergence of the microextrusion systems effectively created a low-cost bioprinter niche, the inkjet printers have mostly remained in the high-end bracket of the bioprinter market. Today, only a few droplet-based models qualify for our definition of low-cost machines. These are shown in Supplemental Figure S2 and discussed in detail below.

FUJIFILM Dimatix’s DMP-2850. FUJIFILM Dimatix is one of the world’s largest suppliers of inkjet printing technology based in the United States. The company was formerly known as Spectra Inc. when it was founded in 1984. It was...
acquired by the Japanese FUJIFILM Holdings Corporation in 2006 and became known as Fujifilm Dimatix Inc. The company focuses on designing, developing, and producing PDOD print heads in tandem with providing 3D bioprinting systems. FUJIFILM Dimatix’s DMP-2850 (formerly DMP-2000), released in 2009, is one of the only few drop-based printers that falls into the low-cost category. It includes a drop watcher, fiducial cameras, a PC, and drop manager software. This printer is highly compact (W × D × H dimension: 67 × 58 × 42 cm³) and can fit in any standard BSC/fume hood. It is compatible with various substrates, such as glass slides, petri dishes, and multilayer plates. Moreover, the machine can handle a large build volume of up to 20 × 30 × 2.5 cm³ at ±25 µm unidirectional repeatability. The vacuum platen’s (which secures the substrate in place) temperature can be adjusted up to 60 °C. The printer’s fiducial cameras provide the DMP-2850 with many advantages, such as alignment using reference marks, positioning of the print’s origin to match the substrate’s positioning, measurement of resulting features and their locations, image capture and inspection of the printed pattern or drops, cartridge alignment when using multiple ones, and matching drop placement to a previously patterned substrate.\(^{161}\)

The DMP-2850 uses microelectromechanical system (MEMS)-based disposable cartridges of 1.5 mL usable volumes, which allows users to fill their own media-like bioink or hydrogel–cell suspensions. The MEMS-based disposable cartridge has 16-nozzle heads with 254 µm spacing in a single row, with a drop volume available in either 1 or 10 pL. With the 1 pL nozzle, one can deposit features as small as 20 µm in size, making it suitable to aid the fabrication of microelectronic devices, as well as DNA patterning in biotech applications. Furthermore, the droplets coming out from the nozzle can be fine-tuned using a built-in waveform editor and monitored using the drop-watch camera.\(^{162}\)

As shown later in Figure 6, FUJIFILM Dimatix’s DMP-2000 series printer has had a significant impact on academic research, with almost 670 hits resulting from our keyword search using Google Scholar since 2006. Notably, this is even more impactful in facilitating basic scientific research than many of the high-end bioprinters that we have surveyed, and the machine is undoubtedly the uncontested winner within the low-cost market segment. However, the DMP-2000 series printer is one of the few products that have been on the market for a long time (since 2005, to be exact); therefore, this is also one of the reasons contributing to why this product is more highly cited than those of the competitors. Furthermore, it is difficult to isolate how many of these citations belong to the bioprinting applications, given that the machine is also used for MEMS fabrication. Nonetheless, it currently stands as the most impactful low-cost model out there.

**MicroFab’s jetlab 4 and jetlab 4xl.** MicroFab is a U.S. company that has been providing piezoelectric inkjet-based dispensing instruments since 1984. The company’s focus is primarily on the research and development of inkjet solutions that meet the microdispensing requirements of a wide variety of large and small customers. For example, MicroFab has successfully demonstrated droplet-based printing with more than 500 specialty fluids, ranging from gases at cryogenic temperatures to melted solder at over 300 °C.\(^{163}\) The company also provides hardware customizations such as single-fluid (one-nozzle) or four-fluid (four-nozzle) print heads with various heating, filtering, and orifice (e.g., 20–80 µm diameter) configurations, and bio-ink cartridge volumes ranging between 0.5 and 30 mL, with an optional stirring capability. In 2006, it introduced a line of inkjet printers called jetlab 4. Within the series, there are four models that are available at different price ranges. However, only the jetlab 4 and jetlab 4xl have price tags that are within the upper boundary of the low-cost bioprinter category.

Both of the jetlab 4 models are equipped with a CCD camera for droplet observation, an enclosure chamber (without a HEPA filter), and a panel PC. The Z-height adjustment of the print head and the pneumatic control must be done manually. The print heads for all models can operate with the same travel speed of 5 cm/s (15 cm/s² acceleration) and can deposit bio-ink in two printing modes: print on-the-fly (straight and/or curved in any direction) or point-to-point. The jetlab 4 is capable of printing a 16 × 12 cm² area at ±30 µm positioning accuracy and ±20 µm repeatability. The CCD camera on the jetlab 4 is mounted at a 15° angle for drop impact observation and coarse substrate alignment. The jetlab 4xl is basically an upgraded model of the jetlab 4 to handle a larger build area of 21 × 26 cm². Additionally, the CCD camera on it is mounted on an XY stage for horizontal drop observation, which gives the jetlab 4xl more options to work with MicroFab’s high-temperature and multichannel print heads.

The jetlab 4 models have been used in more than 23 countries, and they have been highly impactful in the research field with ~85 citations (Fig. 6). For example, they are used to print silk fibroin, a material for biomedical devices;\(^{164}\) cell-laden poly-l-lysine mixed with fibronectin;\(^{165}\) PLA;\(^{166}\) the conductive polymer composite PEDOT:PSS;\(^{167}\) pattern polyethylene glycol (PEG) and polymethyl methacrylate (PMMA) on a carbon-fiber mesh;\(^{168}\) and UV-curable silicone elastomers.\(^{169}\)

**Light-Based Bioprinting Technology**

There are two main light-based technologies that commonly appear in the commercial 3D bioprinters listed in Suppl. Tables S1 and S2: The first is digital micromirror device (DMD)-based 3D printing technology (aka stereolithography),
which is a layer-by-layer photo-crosslinking technique (Fig. 5a,b). Specifically, this printing method uses a dynamic mask generated by the DMD chip. The mask contains a 2D pattern that represents each cross-sectional layer of the desired 3D construct. A laser source is then projected from the DMD chip into a vat containing a photocurable biomaterials with or without cells. This can be done through either the bottom (Fig. 5a) or top (Fig. 5b) of the vat. The material is then polymerized within a single layer on an automated build platform/substrate. After each layer is solidified, the platform/substrate is moved up or down and another layer is then built below or on top in a similar manner. The second is laser-assisted droplet-based bioprinting technology, which is a light-based drop-on-demand bioprinting method (Fig. 5c). This technique uses laser energy to transfer cell droplets from a thin film of bio-ink, contained on an energy-absorbing donor surface (e.g., titanium or gold ribbon), to a receiving substrate. The droplet transfer occurs via a propelling pressure force from a rapid formation of a bubble, which in turn is created by vaporization of the donor material. The print patterning is controlled via a digital scanning mirror that directs the laser beam to targeted locations (see the “MicroFab’s jetlab 4xl-A, jetlab 4xl-B, and jetlab II” section for further discussion of the laser-assisted bioprinting platforms).

There are currently only two DMD-based 3D bioprinters on the market that we could find, both of which fall into the low-cost range (see the “Low-Cost Light-Based Bioprinters” section). In comparison to the other two printing methods (i.e., microextrusion and inkjet), discussed in the “Microextrusion-Based Bioprinting Technology” and “Droplet-Based Bioprinting Technology” sections, the light-based 3D printing technology is the most advanced method because it is capable of rapid fabrication of 3D cellular structures with both high resolution (~20–50 µm)\textsuperscript{153} and cell viability (75%–90%). It has the additional advantage that it is compatible with any photocurable bio-ink, regardless of the material’s viscosity.\textsuperscript{18} Therefore, it is possible to fabricate viable high-cell-density constructs with high precision, and without the need to worry about damage from shear stresses (like with microextrusion). However, the light-based 3D printing methods are limited by the fact that the bio-ink/cells (if any) must be loaded into the printing bed a priori. This means that although the crosslinking can be done at any desired location, the cell/bio-ink’s positions can only be manipulated by combining the DMD with a secondary technology (e.g., microextrusion) either before or during the printing process. Otherwise, any changes to the bio-ink must be done by manually replacing the contents of the print bed.

Low-Cost Light-Based Bioprinters

Supplemental Figure S3 shows photographs of all low-cost DMD-based 3D bioprinters listed in Supplemental Table S1.

CELLINK’s Lumen X 3D Bioprinter. Lumen X is another affordable benchtop 3D bioprinter released in 2019 by CELLINK. This was done in collaboration with Volumetric, a U.S.-based start-up. Unlike the other extrusion-based 3D bioprinters from CELLINK, Lumen X is a digital light processing (DLP) bioprinter that enables high-speed light-based crosslinking, which has been shown to be 50 times faster and more consistent than extrusion-based machines. The projected light wavelength used in the Lumen X is 405 nm. Additionally, CELLINK and Volumetric also offer their proprietary GelMA Photoink bio-ink, whose curing speed has been optimized to have little to no impact on cell viability. This enables the printing of various bio-inks, such as cell-laden hydrogels/microfluidics and macroporous structures.

Furthermore, the machine can achieve a feature resolution of ~50 µm in the XY plane, while the Z resolution of 5
μm is dictated by its stepper motor. It takes approximately 10 s to crosslink each XY layer. The max build volume is 6.5 × 4 × 5 cm³, which means that this machine can also be used to construct lab-on-a-chip microfluidic devices. Also, its build platform is small. Therefore, the printing can be performed inside a 10 cm petri dish in order to minimize the amount of bio-ink needed per job. Moreover, the build platform is designed with a quick-release mechanism that makes it easier to swap for a new one. Additionally, CELLINK offers two different options for improving the adhesion of the printing construct to the print bed: a glass build platform for working with hydrogels and a metal build platform for working with resin-based materials.

Overall, the Lumen X is a very compact machine (W × D × H dimension: 24 × 43 × 41 cm³) that can fit into any BSC for a sterile bioprinting process. It has been used for fabricating highly complex tissue structures, such as hydrogels with functional vascularized alveoli, implantable hepatocytes in a prevascularized hepatic hydrogel, a hydrogel scaffold with the controlled spatial distribution of bioactive molecules along aligned microchannels for neurite outgrowth in brain tissue generation, and 3D patient-specific models of a developing human heart.

Allegro 3D’s STEMAKER Model D 3D Bioprinter. Stemker Model D is a DLP bioprinter from a U.S.-based company called Allegro 3D. The printer is designed for high-throughput automated printing directly in multiwell (e.g., 6-, 12-, and 24-well) plates. The latter minimizes product damage and/or contamination by eliminating the need to transfer the resulting products from the printer to a culture dish. Furthermore, the STEMAKER Model D offers rapid bioprinting at a 1000× faster speed and a 10× better resolution (~10 μm) than the traditional extrusion-based bioprinters. Thus, this machine enables high-throughput tissue printing within a very short turnaround time.

Like the Lumen X from CELLINK, the STEMAKER Model D also uses the 405 nm light for photocuring projection. Furthermore, it has a compact design (W × D × H dimension: 45 × 36 × 44 cm³), allowing it to fit into all major BSC models. Additionally, the STEMAKER Model D utilizes a built-in computer and a 10-inch glove-friendly touch screen. The machine supports .stl files, which can be loaded through a USB port. The user can then specify the working locations in each of the multiwell plates, as well as the individual printing parameters (e.g., light intensity, printing speed, and section height) for each one.

Additionally, the STEMAKER Model D has temperature control (RT through 60 °C) to provide optimal thermal printing conditions for specific bio-inks. The company also sells glass-bottom-coated multiwell plates for high-resolution imaging and better adhesion of the 3D printed tissues. Multiple other bio-inks and 3D printed parts are also available for sale on Allegro 3D’s website. In terms of the Model D’s applications, it is worth noting that Allegro 3D reported a successful fabrication of an induced pluripotent stem cell (iPSC)-derived human liver tissue that mimics the hepatic lobule microarchitecture.

Brief Overview of the High-End 3D Bioprinters

According to Figure 6, the high-end printers are more popular than the low-cost ones among the research community. This can be attributed to several reasons: (1) they were the first on the market and have thus benefited from a longer adoption time; (2) these machines may be housed by shared facilities, thereby making them more accessible to users who would not otherwise be able to afford them; and (3) some of the manufacturer companies also provide printing services to customers who choose not to buy their own hardware. For example, such customers can rent the system for less than 50% of the cost without having to commit to a purchase. Alternatively, the companies may support the customers’ fund-raising efforts (e.g., grant writing) for a printer’s purchase. In fact, together these strategies provide significant advantages over buying low-cost printers, considering that the latter are newcomers to the market and their performance has not yet been characterized by the user. Therefore, in order to provide a comparison of how low-cost bioprinters measure up to those from their high-end competitors, the following section reviews the latter in more detail.

Furthermore, it is expected that some of the high-end technologies may trickle down to low-cost machines in the near future. This makes it even more important to understand the high-end technologies to forecast the upcoming low-cost printer trends. To that end, this section summarizes the technical characteristics of the high-end bioprinters that are currently available on the market.

High-End Microextrusion-Based Bioprinters

As shown in Figure 6 and Supplemental Table S2, EnvisionTEC and RegenHU are currently the top 2 manufacturers that provide the most popular high-end microextrusion-based bioprinters on the market. In this section, we give a brief overview of these two companies, their products, and their uniqueness in a brief comparison against other products in the same price category. It is important to mention that there are other high-end companies on the market, but it is not the intent of this paper to review all of them. Instead, we chose a few representative examples to compare and contrast the advantages that the customers get by investing more in high-end products versus low-cost bioprinters.

EnvisionTEC’s 3D Bioplotter Starter, Developer, and Manufacturer. EnvisionTEC is one of the largest players in the 3D printer manufacturing industry, with headquarters in
Germany. It has been in operation since 2020, has more than 250 employees, and accounts for roughly a quarter of the 3D bioprinter market. The company’s size can partly be attributed to the fact that EnvisionTEC does not solely deal with the 3D bioprinting sector but also is involved with various nonbioengineering 3D printing. Some of these include medical devices, hearing aids, dental, orthodontic, jewelry, aerospace, and automotive. The company offers three models of the 3D Bioplotter bioprinters: 3D Bioplotter Starter, 3D Bioplotter Developer, and 3D Bioplotter Manufacturer. All three models employ pneumatic extrusion print heads. However, the Developer and Manufacturer have modular temperature-controlled (both in the parking position and during the printing process) and UV crosslinking print heads. Also, the Developer is capable of operating with up to three modular simultaneous print heads, and the Manufacturer with up to five (Suppl. Table S2). Conversely, the Starter has only two fixed heated print heads. Therefore, it is less customizable than the Developer or the Manufacturer, due to its lack of modularity.

Another significant difference between the three models is the level of available automation that comes with the printer; for example, the Starter only has an automated nozzle cleaning feature, while the material calibration and print bed height control are manual. In contrast, the Developer has an automated Z-height adjustment and nozzle cleaning, but its material calibration is still manual, and it has no photographic logging of the layer inspection during the printing. Finally, the Manufacturer is the most automated of the three; it has a substrate height sensor, a finely tuned temperature-controlled build platform, four external temperature sensor ports, a semiautomatic camera-assisted material calibration, an automated nozzle cleaning mechanism, and a background recalibration of the critical hardware settings during regular use.

The Biplotter series is designed to work in both cooled (as low as –10 °C) and heated (80 °C) environments and is compatible with a wide range of materials, including thermoplastics (e.g., PLA, PCL, poly-l-lactide acid (PLLA), polyurethane (PU) and ABS), hydrogels (e.g., agar, alginate, chitosan, and gelatin), and ceramic/metal pastes (i.e., HA, titanium, and tricalcium phosphate). Some applications of these machines include bone regeneration, drug release, tissue fabrication, and materials science. Overall, the EnvisionTEC bioprinters have turned out to have the most significant scholarly footprint, yielding ~960 hits in our scientific literature search (Fig. 6). Yet, despite the many advantages, they are not equipped with a built-in sterile chamber but are instead meant to be used inside a biohood.

RegenHU’s R-GEN 100 and R-GEN 200. Like the EnvisionTEC, RegenHU is also one of the largest players in the 3D bioprinting market. The company was founded in 2007 and is headquartered in Switzerland. However, unlike its competitor, RegenHU is much a smaller company, with about 20 employees, and it focuses on producing hardware and software exclusively for bioprinting. Therefore, RegenHU’s products provide a very powerful solution for tissue fabrication with a series of bioprinting workstations.

Until the fall of 2020, RegenHU’s most popular models were the BioFactory (discontinued in early 2020) and the 3D Discovery Evolution. These two professional systems were meant to accommodate both the high-throughput demands of the manufacturing industry and the small lab-scale environment of academic tissue engineering research and development. However, recently RegenHU has upgraded its product line by introducing two brand-new models: a lab-scale compact tabletop R-GEN 100 and a bigger R-GEN 200. These are fully customizable with multiple modular print head technologies available in a single 3D bioprinting platform, such as a pneumatic strand dispenser, a pneumatic drop dispenser, a pneumatic melt dispenser with or without an electrowriting module, a volumetric strand dispenser with or without an electrowriting module, a light curing tool, and a microscope tool. Both the R-GEN 100 and R-GEN 200 have five available tool slots for housing these print heads, which enables them to build a range of simple and complex constructs.

Moreover, their work zone (i.e., print bed) comes in four different options: standard, electrowriting and spinning, physiological temperature (5–40 °C), and high temperature (RT through 80 °C). While the standard configuration has no temperature control and the electrowriting and spinning come with built-in heating, the two latter options require an external liquid temperature control unit. This unit can also be used to control the temperature of the bio-ink cartridges and the extrusion nozzles. Thus, the R-GEN 100 and R-GEN 200 are compatible with a wide range of bio- and nonbiomaterials, like Collagen, elastin, alginate, cellulose, hyaluronic acid, silk fibroin, gellan gum, chitosan, peptide gels, decellularized extracellular matrix (ECM), graphene, gelatin, Matrigel, PEG, gelatin methacryloyl (Gel-MA), methacrylated hyaluronic acid (HAMA), photocurable silicones, poloxamer, polyvinylpyrrolidone (PVP) and carbone nanotubes. Furthermore, the R-GEN 100 comes with a HEPA filter, while R-GEN 200 has a Class II BSC. Therefore, both provide sterile conditions for printing cells and/or cell-laden materials.

Overall, RegenHU’s bioprinters have seen extensive use in research over the last few years. Their products have been cited ~600 times (Fig. 6); for instance, they were used to evaluate the material parameters in a time-pressure dispensing system, test an alginate sulfate–nanocellulose bio-ink, evaluate the transdermal penetration of nanoparticles, and test peptide-based hydrogels as a material for tissue engineering.

Main Advantages over the Low-Cost Microextrusion-Based Bioprinters. As mentioned previously, we have chosen not to
focus on the reported resolutions of the bioprinters because (1) they are often reported in different ways, making it difficult to draw a fair comparison; and (2) they are rarely achievable in a practical setting by the nonexperts. We will simply state that in our experience, the high-end companies appear to be more transparent about their positioning accuracy and printing resolution claims, which makes it likelier that their product can achieve what is promised. Aside from this, the following are the major differences that we observed between the low-cost and high-end microextrusion printers.

1) **All-in-one modular design capable of multiprinting techniques**: This observation is closely related to the trend above, because the sockets/mounting slots are needed in order to switch out modules. Based on Supplemental Tables S1 and S2, most of the high-end microextrusion-based bioprinters have a modular structure and work with modular print heads that are capable of handling multiple materials and/or utilize different printing technologies simultaneously (e.g., thermal plastic extrusion, pneumatic extrusion, mechanical extrusion, inkjet, and melt electrospinning-writing). This combination of multiple technologies in a single platform enables the high-end printers to fabricate more complex products; for example, tissue engineering scaffolds can be made out of multiple materials using the thermoplastic extrusion first and then seed with cells using inkjet later, or multiple microextruders could be used to fabricate intricate tissue patterns using multiple bio-inks. However, this ability to perform both extrusion-based and droplet-based printing simultaneously is also the main factor for hardware’s higher price. Nonetheless, the same trend has also begun to appear in some of the low-cost models that were recently released in 2020, for example, the 3D BioPrinter by Brinter and AXO A1 through AXO A6 bioprinter series from Axolotl Biosystems.

2) **Multiaxial printing**: A common limitation of the low-cost microextrusion bioprinters is that their
motion is limited to the XYZ directions; however, this often necessitates the use of undesirable support structures to prop up the object that is being printed. To overcome this constraint, some of the high-end companies equip their machines with additional degrees of motion, such as rotation. For example, Advanced Solutions Inc.’s BioAssemblyBot printer comes with a six-axis robotic arm that has eight independent syringe barrels. Not only does the arm eliminate the need for making support structures, but also it gives the BioassemblyBot the ability to print on nonplanar surfaces at different angles (e.g., into an in vivo wound site). Additionally, the arm can be customized with several modules, including a UV crosslinker, heated print heads, and dual-component extruder.

3) **Integrated hardware and accessories:** As a result of our survey, we have found that the inclusion of an enclosed sterile chamber with a HEPA filter and a UV-C disinfection lamp does not account for the main price difference between the high-end and low-cost models. A case in point is the high-end bioprinters from EnvisionTEC, GeSiM, and 3D Bioprinting Solutions that do not utilize a sterile chamber because they are meant to be compact models that can easily fit into most BSCs. On the other hand, the inclusion of a full-sized class II BSC (like in the case of RegenHU’s R-GEN 200) could very well be a major contributor to the printer’s cost due to the bulkiness of the equipment. Overall, however, we conclude that the majority of the price differences between the high-end and low-cost bioprinters can be explained by the inclusion of advanced integrated hardware, such as a microscope, control PC, wide range of temperature-controlled print beds and/or print heads, and automation. Therefore, the customers should make a cost–benefit analysis as to whether these features are truly worth it to them.

4) **Company reputation:** Another major difference between the low-cost and high-end printers are the companies that make them. In the case of the former, they are mostly small-scale start-ups, while the high-end printers are mostly made by established industry leaders. This can affect the logistics of purchasing and maintaining the printer. For example, a more established company is likely to exist longer and provide better customer and technical support, and their machines tend to be better made. In contrast, a small start-up may delay the delivery of the printer, their customer support could be lackluster, and their machines could break down more frequently. Finally, there is a big risk that the smaller company could simply go out of business, leaving the customer without any support at all. Having said that, the recent explosion of the low-cost market segment will surely drive down the prices of the established competition in the near future.

### High-End Droplet-Based Printers

**MicroFab’s jetlab 4xl-A, jetlab 4xl-B, and jetlab II.** According to **Figure 6**, MicroFab’s droplet-based bioprinters are the most highly cited machines among the other inkjet printers in the research field. Since its founding in 1984, the company has become one of the world’s leaders in PDOD technology (see **Fig. 4a** and the “Low-Cost Droplet-Based Bioprinters” section). The high-end bioprinters offered by MicroFab come in three models: jetlab 4xl-A, jetlab 4xl-B, and jetlab II. The first two are essentially improved versions of the low-cost jetlab 4 and 4xl machines (see the “Low-Cost Droplet-Based Bioprinters” section). Specifically, they have been upgraded with a HEPA filter and blower for sterile bioprinting, a motorized Z stage, an electronic pressure/vacuum regulator, a fiducial camera for substrate alignment and measurements, and an integrated ultrabalance for calibration (available only for the jetlab 4xl-B). Additionally, their positioning accuracy and repeatability were improved to ±2 μm and ±5 μm, respectively, and the printers have been made compatible with the various MicroFab modular print head options.

The jetlab II is the most expensive of the three models due to its higher level of automation, larger print area, linear motorized stages that provide precise positioning (±4 μm accuracy and ±2 μm repeatability), and a fast travel speed of 10 cm/s (40 cm/s² acceleration). The highly automated features of this model include electronic pressure control, jet alignment, and an inspection option that works through image analysis. The jetlab II has been used for various applications like developing a new inkjet printing approach for the facile fabrication of microscopic arrays of biocompatible silk nest arrays for cell hosting;¹⁹³ studying fast, flexible inkjet printing methods for patterning dissociated neurons in culture;¹⁹⁴ micropatterning living cells into a cell culture medium by co-printing different cells into various designs, such as complex gradient arrangements;¹⁹⁵ creating printed dual cell arrays for multiplexed sensing;¹⁹⁶ and developing inkjet-based cell printing with a 30 μm nozzle diameter for cell-level accuracy.¹⁹⁷

**Microdrop Technologies GmbH’s Autodrop Bioprinters.** Microdrop Technologies GmbH is a Germany-based company founded in 2005 with less than 100 employees.¹⁹⁸ Like MicroFab, Microdrop Technologies is another leader in inkjet printing applications and advanced microdispensing technologies. It offers the following droplet-based models: Autodrop Compact, Autodrop Gantry II, and Autodrop Gantry. The Autodrop Compact has a relatively large build
volume (21 × 21 × 11 cm³) with a ±25 µm accuracy, a ±10 µm repeatability, and a travel speed of 7.5 cm/s (50 cm/s² acceleration). Compared with the Compact model, the Gantry II and Gantry models have larger printable areas of 30 × 30 × 10 cm³ and 36 × 60 × 10 cm³, respectively. Furthermore, the Gantry II has an improved repeatability of ±3 µm and a faster travel speed of 10 cm/s (100 cm/s² acceleration). Meanwhile, the Gantry model comes with the best positioning: a ±10 µm positioning accuracy, a ±3 µm repeatability, and the highest travel speed of 50 cm/s (100 cm/s² acceleration).

Furthermore, the Autodrop systems use exchangeable nanojet dispenser heads with piezo valves, or picoliter dispensing pipettes, for compatibility with a wide range of material viscosities (0.4–10,000 mPas) and droplet volumes (0–380 pL). This makes them suitable for many applications, such as studying the effect of biocompatible surfactants on PDOD inkjet printing of living cells in order to improve the reliability of droplet formation and cell viability; developing a new approach to inkjet printing of single-cell cultures using a liquid hydrophobic barrier that prevents sample dehydration and enables spatially addressable arrays for statistical quantitative single-cell studies; developing large-scale size-controlled pancreatic progenitor cell clusters as a potential cell-based therapy for diabetes; studying reversible calcium alginate hydrogel porogen beads for direct control of macropore size on a scale relevant to cell culturing and tissue engineering; and fabrication and testing of an aptasensor with printed poly(3,4-ethylenedioxythiophene) polystyrene sulfonate electrodes for influenza A virus detection. Overall, the Autodrop systems have been used widely in research, with 89 hits generated by a Google Scholar search (Fig. 6).

Additionally, Microdrop Technologies GmbH offers nanojet dispenser heads with a microsolenoid valve (Fig. 4b) that has a dispensing volume of 50 or 300 nL. Specifically, the droplets in this case are formed at the nozzle’s tip through a combination of a syringe pump and the high-speed microsolenoid valve attached to the print head. Compared with the other inkjet technologies, the minimally invasive nature of the microsolenoid valve technology yields one of the highest cell viabilities on the market of 95%.

**Digilab’s Celljet Live Cell 3D Bioprinter.** Similarly, the Celljet Live Cell 3D Bioprinter, produced by a U.S.-based company, Digilab Inc. founded in 2001, is another high-end droplet-based option that employs solenoid valve nanojet dispensing technology for droplet generation with a liquid delivery range from 10 nL to 1 mL. The Celljet Live Cell Bioprinter is capable of holding up to 16 individually addressable channels at a time, which are designed for high-throughput manufacturing with a very high positioning accuracy (±1.3 µm) and repeatability (±10 µm). Therefore, the Celljet is mostly used for live cell bioprinting studies for high cell viability and evaluation of bio-ink properties in the 3D bioprinting process, with around 20 hits resulting from our keyword search using Google Scholar (Fig. 6).

**Main Advantages over the Low-Cost Droplet-Based Bioprinters.** The following are the significant differences between the low-cost (see the “Low-Cost Droplet-Based Bioprinters” section) and high-end droplet-based bioprinters uncovered as part of our survey:

1) **Superior positioning:** Nozzle positioning is needed for achieving a fine printing resolution. The low-cost jetlab 4 and jetlab 4xl have ±30 µm positioning accuracy and ±20 µm repeatability, while high-end models like the jetlab 4xl-A and 4xl-B have a higher positioning accuracy (±20 µm) and repeatability (±5 µm). Likewise, all of the high-end droplet-based printers from Microdrop Technologies provide superior positioning compared with the low-cost models; for example, the Compact model has a ±25 µm accuracy and a ±10 µm repeatability, the Gantry II has a ±25 µm accuracy and a ±5 µm repeatability, and the Gantry has a ±10 µm accuracy and a ±3 µm repeatability. Among all the high-end droplet-based bioprinters, the jetlab II has the most superior positioning, with a ±4 µm accuracy and a ±2 µm repeatability. Finally, the Celljet Live Cell Bioprinter by Digilab Inc. is another example of a high-end model with superior positioning accuracy (±1.3 µm) and repeatability (±10 µm).

Another interesting observation is that none of the low-cost models come with a motorized Z stage, while all the high-end droplet-based bioprinters come with a software-controlled XYZ-axis system.

2) **Larger build space:** Large build areas are critical for being able to print many objects on the same bed, while the maximum height of a product is key to making thick tissues. A representative low-cost bioprinter, DMP-2850 by FUJIFILM Dimatix, has a build volume of up to 20 × 30 × 2.5 cm³. In contrast, the high-end Autodrop Compact, Gantry II Family, and Gantry models have larger build printable areas of 21 × 21 × 11 cm³, 30 × 30 × 10 cm³, and 36 × 60 × 10 cm³, respectively. Specifically, the high-end models can build products that are ~4× higher in the Z direction relative to the low-cost models. Similarly, the print areas of the high-end jetlab models (e.g., up to 30 × 30 cm² for jetlab II) are also larger than the 16 × 12 cm² build area of the low-cost jetlab 4.

3) **Faster print head travel:** Rapid fabrication is necessary for high-throughput manufacturing. For
comparison, the low-cost jetlab 4 and jetlab 4xl have a printing speed of 5 cm/s, while the high-end jetlab II has a print head travel speed of 10 cm/s. Similarly, the Autodrop Compact has a travel speed of 7.5 cm/s, and the Gantry II has a travel speed of 10 cm/s. Finally, the Gantry model has the highest travel speed of 50 cm/s.

4) **Sterilized printing environment with a HEPA filter:** The ability to maintain a sterile environment is key to preventing contamination and infections in the resulting bioprinted products. However, most of the droplet-based printers are too bulky to fit into a conventional BSC. Only the low-cost DMP-2850 and the high-end Celljet Live Cell 3D Bioprinter are compact enough for that, and only Inventia’s Rastrum comes with a built-in sterilization system in its base configuration. Therefore, most of the other printers require the purchase of a sterilization chamber/HEPA filter add-on. For low-cost inkjet models, that means being pushed into the high-end spectrum because their base prices are already borderline with the price threshold (Fig. 2). Therefore, a high-end price for these printer types means being able to print in a sterile environment, which is a critical advantage over the low-cost configurations.

**High-End Light-Based Printers**

**Poietis’s NGB-R.** Poietis is a company that was founded in 2014 as a spin-off from the INSERM Research Institute and the University of Bordeaux, France. It has about 35 employees and holds more than 52 patents. Among some of the products that it sells is a printed human skin model called Poieskin, which some of the world’s leading companies, like L’Oréal, Servier, and BASF, use for cosmetics and pharmaceutical in vitro testing purposes. Poietis currently offers two 3D bioprinter models: NGB-R is intended for small lab-scale research, and NGB-C is designed for large-scale manufacturing (so it is not discussed here). These are the only two bioprinters on the market that use laser-assisted droplet-based bioprinting technology (see the “Light-Based Bioprinting Technology” section), to which the company holds worldwide exclusive intellectual property rights.

Laser-assisted droplet-based bioprinting technology was already briefly discussed in the “Light-Based Bioprinting Technology” section and shown in Figure 5c. The detailed description is as follows: Per Figure 5c, the printing is accomplished by loading the desired concentration (up to 100 million cells/µL) of bio-ink on a donor plate/ribbon. After that, the cell droplets are formed by pulses of laser energy and are transferred to the substrate via pressure buildup in the resulting bubbles. The laser beam is directed via a fast scanning mirror to deposit the droplets in a predetermed pattern with a rapid printing speed of up to 10,000 drops/s.

The advantage of this technology is that it allows the controlling of numerous parameters, like cell concentration, droplet volume/size, printing pattern/deposition location with high precision, repeatability, and reproducibility of the process. Additionally, the fact that it is a nozzle-free technique means that the cells are not damaged by flow shear stresses, compressive forces of extrusion, or phototoxicity. In fact, it has been shown that the cell viability using this printing method is above 95%. Furthermore, the number of cells per droplet can be controlled for achieving a single-cell resolution, and the droplet volume is also tunable from picoliters to nanoliters. Ideally, about 1–100 cells/droplet can be printed at a ~10 µm precision using this technology. However, one drawback of this printing technique is that the compatible bio-ink viscosities are limited to 1–300 mPa/s.18

Based on our market search, the NGB-R is one of the most expensive 3D bioprinters on the market. However, this may be because the machine is an all-in-one bioprinting platform that comes with a six-axis robotic arm (for precise automated motion), a class II BSC, a control panel with a large touch screen, and so forth. Furthermore, in addition to the droplet-based technology, the NGB-R can be equipped with up to three extrusion-based and/or microvalve printing heads. There are also several customizable options for UV crosslinking/photopolymerization, thermal regulation, a cellular-level microscope, and so on.

Some of the applications that the NGB-R has been used for include the creation of a high-cell-density printed tissue,204 cell patterning studies for organotypic,205 and printing mesenchymal stroma cells for in vivo bone regeneration studies.206 However, according to Figure 6, Poietis’s NGB Systems are not highly cited (our Google Scholar survey turned up just five publications) in the research field. This is likely due to the machine’s cost being prohibitive to many academic labs. In line with that logic, it can be speculated further that most of Poietis’ customers are industrial and do not publish their results as much.

**High-End Microfluidics-Based Printers**

**Aspect Biosystems’ Lab-on-a-Printer RX1.** Aspect Biosystems, founded in 2013, is a privately held company based in Vancouver, Canada, with about 49 employees,207 that is pioneering microfluidics-based lab-on-a-printer technology. It has received a $1 million investment from Genome British Columbia,208 and was involved in a $2.2 million project seeking to find new treatments for cancer in collaboration with two of the world’s largest pharmaceutical companies: Merck and GlaxoSmithKline.209 The innovation behind its RX1 3D bioprinting platform is that it uses microfluidic
devices for bio-ink extrusion (see Fig. 7a for a simplified schematic of the concept) instead of the more conventional syringe. Specifically, these heads are essentially PDMS chips that contain multiple micron-sized inlet channels, each of which is individually controlled by pneumatic Quake-style microvalves (Fig. 7b). Specifically, a bio-ink is flowed through the device as a laser from below polymerizes a single layer of a DMD-patterned image projected onto a substrate above. The crosslinking light passes through a transparent flexible membrane, which enables the substrate to move in the Z direction in order to shift the focal plane of the printer. After each layer is finished, the microfluidic chip is moved up (i.e., away from the laser), and a washing fluid is passed through it before a subsequent layer is built in a similar manner.

Figure 7. Illustrations of the different types of microfluidic print head technologies currently used in 3D bioprinters. (a) A microfluidic extrusion print head that draws different types of bio-ink from multiple storage sources via pneumatic pressure. The technology is capable of combining the materials in varying ratios and morphologies (e.g., core–shell) via on-chip valves. (b) Microfluidic hydrodynamic confined flow technology with one outflow channel in the center for bio-ink extrusion and two inflow ones at the sides for recirculating any excess extruded bio-ink back into the nozzle. The cells are deposited only when the liquid probe comes into contact with the substrate. (c) A bioprinting technology that uses a microfluidic chip as a photo-crosslinking print bed (instead of as a nozzle). Specifically, a bio-ink is flowed through the device as a laser from below polymerizes a single layer of a DMD-patterned image projected onto a substrate above. The crosslinking light passes through a transparent flexible membrane, which enables the substrate to move in the Z direction in order to shift the focal plane of the printer. After each layer is finished, the microfluidic chip is moved up (i.e., away from the laser), and a washing fluid is passed through it before a subsequent layer is built in a similar manner.

Not only does this unique printing approach allow the machine to work at fast speeds while maintaining high cell viability, but also it enables it to have precise control over the bio-ink deposition with a nearly single-cell printing resolution. Additionally, the microfluidic heads can be used to mix multiple materials in a continuous manner with concentration profiles that can be programmed to change over time. This “on-the-fly” printing avoids time-consuming bio-ink substitutions and favors the chemical crosslinking of the mixed materials. Moreover, the chip can also serve as a multiplexer that is capable of merging laminar flows in a controlled ratio. This allows for various extrusion styles to be made available using this system programmatically, for example, cell encapsulating droplets; a dual filament composed of two different nonmixed materials, with a discrete boundary between them (as shown in Fig. 7b); or a core–shell structure used to create a protective sheath around a bio-ink filament, in order to preserve the phenotype and functionality of the extruded cells by minimizing their exposure to shear stresses. Hence, the multitude of capabilities that the microfluidic systems offer opens a range of new possibilities for fabricating organoids, cell-laden or multilayered concentric filaments, and hollow fibers (e.g., capillaries for perfusion).

However, one problem with microfluidic bioprinting today is that the cost of these systems remains higher than that of most conventional bioprinters. Nonetheless, Aspect Biosystems is currently offering collaborative opportunities and help in preparing grant funding applications in order to assist with purchasing its system.

It is also worthy to note that the company uses its printers to make for-sale bioengineered products, such as the 3DbioRing—an extremely customizable and physiologically relevant muscle tissue platform that exhibits highly physiological contraction and relaxation responses in an in vitro setting. This makes Aspect Biosystems more versatile than just a hardware company, which in turn increases the likelihood of its continued financial stability and innovation in the microfluidic bioprinting space.

**FluiCell AB’s Biopixlar.** FluiCell AB is a ~20-employee Sweden-based company spun off from the Chalmers University of Technology (Gothenburg, Sweden) to become an independent entity in 2012. It has mainly focused on providing platforms for studying single-cell behavior in drug development, cell biology, and tissue engineering. However, in 2014 FluiCell AB also released its first 3D bioprinter, the Biopixlar, which is capable of printing cell suspensions
directly inside of the culture media/buffer, without the need for any supporting gel or matrix biomaterials. The machine is equipped with a three-axis micromanipulation robotic arm and a motorized sample holder stage, which has a high movement precision of ~2 µm. The unit also comes with an integrated inverted bright field/fluorescence microscope that has three fluorescence excitation wavelengths, a 10× objective, a high-sensitivity camera, a heated print head, and an optional UV disinfection light.

For its printing technology, the Biopixlar uses a “microfluidic hydrodynamic confined flow” technology for building biological tissues from individual cells. Specifically, the printer nozzle, in this case, is essentially a microfluidic device whose tip has one outflow channel in the center and two inflow ones at the sides (Fig. 7b). By maintaining a pressure balance between these opposite flows, a free-standing liquid probe is established, which is capable of depositing individual cells onto a focused (~100 mm) spot on a substrate. To draw an analogy, it acts like the ballpoint of a pen: the recirculation of the bio-ink back into the inflow channels collects any unused suspension, which prevents the cells from floating away from the targeted deposition locations. This microscale fluid control enables the Biopixlar to perform a contamination-free precision delivery of the bio-ink, with a low-volume consumption and local control over the cells’ microenvironment.

The print head that contains the microfluidic device consists of a housing, which also holds multiple wells for storing the different bio-inks, cell adhesion enhancement agents, and washing solutions. These chambers are enclosed in a pneumatic solenoid manifold. During the printing process, the cell suspension and/or the attachment agent solution are pressurized to flow through the microfluidic circuit toward the print head’s tip. This is accomplished by actuating the corresponding solenoid valves in the manifold. The printed cells are then delivered through the positive pressure-controlled outflow channel to the substrate, while the unattached cells are recirculated back into a collection chamber inside of the device via the negative pressure-controlled inflow channels.

As shown in a recent publication, the Biopixlar was able to print up to three different cell types for fabricating 2D/3D complex tissue structures at a single-cell resolution. The printing process was shown to have maintained ~96–97% cell viability at 2 h postfabrication and a higher than 99% cell survivability after 24 h, when skin cancer (A431) and epithelial (HaCaT) cell types were used. However, its maximum printing volume is currently limited to the size of the cell loading chambers (~35 µL) on the print heads and is only compatible with bio-ink viscosities less than 500 mPa/s (which is a major limitation if the creation of rigid scaffolds is required by the application). Nonetheless, the technology is one of the unique novel developments in the field of microfluidic bioprinting; its liquid probe is different from the continuous filament extrusion produced by the microfluidic print head of the Aspect Biosystems’ Lab-on-a-Printer RX1, and it is also not similar to the droplet-based bioprinters discussed in the “Low-Cost Droplet-Based Bioprinters” and “High-End Droplet-Based Printers” sections. Therefore, we believe that this technology holds the potential for revolutionizing the low-cost bioprinters of the future.

**Conclusions and Future Projections for Low-Cost 3D Bioprinter Trends**

Recently, there has been an ever-increasing demand for ex vivo biological models for drug and toxicity testing (e.g., cosmetics), driven by both ethical concerns and the high costs of in vivo experiments. Furthermore, companies, universities, and hospitals are in a race to engineer artificial tissues and organs. Bioprinters enable significant time and cost savings by automating the biofabrication process while at the same time offering the advantage of dispensing a range of cells and materials at precise positions dictated by the user. Considering this demand, the high price of professional bioprinters, and the explosion of start-ups trying to fill the low-cost niche, it is expected that high-end technologies will trickle down and become more accessible to everyone. Furthermore, with universities now introducing 3D printing courses, it is also likely that the next generation of the biotechnology workforce will encounter these machines in their jobs. Therefore, it is important to highlight the current bioprinter trends and forecast how the technology will change in the future.

In this paper, we have provided an overview of the currently available commercial low-cost printers that utilize different fabrication technologies: microextrusion-based, droplet-based, light-based, and microfluidics-based. Furthermore, we contrasted them against some of the more expensive high-end models to make projections regarding the evolution of the low-cost bioprinter market. As expected, the low-cost bioprinters remain minimalistic, have lower-quality parts and a poorer assembly, and provide an inferior resolution and less automation than the higher-priced instruments. Most of them use extrusion for the method of dispensing the bio-ink, which results in a roughly similar order of magnitude printing resolution: ~100 microns. However, this resolution appears to be enough for most customers, given that it is comparable to the size of a single cell. A case in point is Figure 8, where we show that prints with quality that is comparable to that of the high-end machines can be achieved using the low-cost models across all three of the main technology types: microextrusion, droplet-based, and light-based.
Figure 8. Product quality comparison between the low-cost and high-end machine models for micro- and macro-sized state-of-the-art applications using each printing technology type. (A) Scanning electron microscopy (SEM) images of scaffolds fabricated using the low-cost Hyrel 3D 30M 0°–90° pattern (A1) and 45°–45° pattern (A2) (scale bars: 1 mm). Adapted from Calore et al.243 with permission from Springer Nature. (B) SEM images of scaffolds fabricated using the high-end EnvisionTEC V1.0 Bioplotter 0°–90° pattern (B1) and 0°–45° pattern (B2) (scale bars: 1 mm). Adapted from Calore et al.243 with permission from Springer Nature. (C) Photograph of a 3D bioprinted human-sized osseous labyrinth fabricated using the low-cost Hyrel 3D Engine HR bioprinter (scale bar: 1 mm). Reproduced from Romanazzo et al.244 with permission from John Wiley & Sons. (D) Photograph of a bioprinted perfusable heart fabricated using the high-end RegenHU 3D Discovery bioprinter (scale bar: 1 mm). Reproduced from Romanazzo et al.244 with permission from John Wiley & Sons. (E) Fluorescent microscopy images of single-cell encapsulating droplets fabricated using the low-cost MicroFab jetlab 4 droplet-based bioprinter on day 0 (E1) (scale bar: 50 μm) and the same droplets with cells that have divided into 3D spheroids on day 1 (E2) (scale bar: 150 μm). Adapted from Ribeiro et al.246 with permission from Ribeiro, R. D., under the Creative Commons Attribution (CC BY) License. (F) Fluorescent microscope images of size-controlled adult pancreatic progenitor cell clusters fabricated using a high-end printer from Microdrop Technique GmbH at varying printing speeds: 10 mm/s (F1), 5 mm/s (F2), and 1.25 mm/s (F3) (scale bar: 50 μm). Adapted from Yang et al.201 with permission from American Chemical Society. (G) Photographs of hollow conical structures bioprinted with sodium alginate, calcium chloride, and NIH 3T3 mouse fibroblasts using the low-cost MicroFab Technologies with 120 μm diameter MJ-ABL droplet-based piezoelectric print heads and a multichannel pneumatic controller: test print of the 3D design (G1), side view (G2), and top view (G3) (scale bars: 2 mm). Reproduced from Sakurada et al.247 with permission from Elsevier Science & Technology. (H) Photographs of hydrogel structures comprising different materials bioprinted using the high-end Inventia RASTRUM droplet-based machine (scale bars: 2 mm). Adapted from Utama et al.248 with permission from the corresponding author, Professor J. Justin Gooding, UNSW, Australia. Note: Due to the low viscosity of the bio-inks used with the droplet-based printers, it is difficult to print macroscopic 3D structures using these machines. (I) Fluorescent images of a bioprinted human liver model fabricated using the low-cost Allegro 3D STEMAKER Model D light-based machine. Hepatic cells are green and supporting (a mix of endothelial- and mesenchymal-derived) cells are red (scale bar: 500 μm). Adapted from Ma et al.249 under the Creative Commons Attribution (CC BY) license. (J) Fluorescent microscopy image of a breast cancer organoid scaffold (green) fabricated using the high-end CELLINK Holograph X light-based 3D bioprinter. The scaffold is showing neovascularization (red with blue nuclei) after being implanted in a mouse for 8 weeks (J1). Fluorescent microscopy image of a vascular bundle structure (blue) with human astrocytes (red with blue nuclei) fabricated using the high-end CELLINK Holograph X light-based 3D bioprinter (J2) (Scale bars: 100 μm). Adapted from Ma et al.249 under the Creative Commons Attribution (CC BY) license. (K) Photograph of vascularized alveolar model topologies fabricated using the low-cost CELLINK Lumen X light-based bioprinter. Red blood cell (RBC) perfusion is shown in red, while the air sac was ventilated with O₂ (scale bars: 1 mm). Adapted from Grigoryan et al.170 with permission from AAAS. (L) Fluorescent microscopy of a vascular bundle structure fabricated using the high-end CELLINK Holograph X light-based 3D bioprinter. HUVEC cells are red and nuclei are blue (L1). Photograph of a large vascular bundle fabricated using the high-end CELLINK Holograph X light-based 3D bioprinter (L2) (scale bar: 500 μm). Figure adapted from CELLINK’s Holograph X brochure (publicly available).
The higher-end machines also tend to offer more automation (e.g., calibration, monitoring/inspection), a larger build space with a superior nozzle positioning and/or multiaxial travel, and HEPA filtration for a sterile onboard environment. Additionally, the high-end manufacturers tend to be established, which translates into faster delivery, better technical support, and a more reliable warranty for the customer. Finally, at least on paper, the printing resolution specifications for these machines are almost identical to those of their low-cost competitors. It is more likely that the high-end models can achieve them in practice due to the high-quality components and more extended optimization.

Nonetheless, we anticipate that the low-cost market will develop vibrantly in the near future. To that end, the following sections outline the major trends that we expect will play a role in the upcoming evolution of this sector.

**Modular Print Heads**

A 3D bioprinting system consists of two main components: the printing tool’s (e.g., nozzle’s) motion and material dispensing/solidifying. While the former is generally an inherent property of the system, the print heads responsible for the latter are becoming “modular.” This means that they can be substituted for other print heads, which use a different bio-ink and/or printing technology, or even carry an additional tool (e.g., a camera, curing light, or fan) all together (Fig. 9). This gives the user enormous flexibility by extending the range of things a single machine can do at a relatively minor additional investment. In fact, in some cases, a set of modular heads is already included with the purchase (e.g., Regemat BIO V1 comes with three mechanical extruders and a filament extruder; DR. INVIVO 4D consists of a mechanical extruder and a filament extruder), while in other cases the users can order what they need as add-ons.

Figure 9 summarizes the state-of-the-art print head technologies, specifically:

- The mechanical/pneumatic extruder print heads (Fig. 9a) typically use disposable syringes of standard sizes (e.g., 5, 10, 30, and 60 cc) as the bio-ink reservoir and their needles as the “nozzle.” In this manner, the user can fully control what and how much bio-ink goes into the syringe, how it is loaded, the sterility of the environment, and the print resolution (by controlling the gauge of the needle), while the print head just plunges the syringe and optionally cools or heats it in order to maintain the bio-ink under desirable conditions (e.g., the physiological temperature of 37 °C).

- The microdroplet/microline extruder print heads (Fig. 9b) are similar to the mechanical/pneumatic extruding print heads, with the exception that they use a cartridge instead of a syringe to store the bio-ink. This is largely because their nozzle must contain a microvalve to create the liquid droplets, and hence the syringe needle cannot be used for depositing the bio-ink. Optional temperature control for the cartridge is also available.

- The hot-melt pneumatic extruder print heads (Fig. 9c) are also similar to the mechanical/pneumatic extruder print heads, except these are typically used for very high-temperature applications, where granules or powders are melted to create the ink. Typically, these types of print heads are used for making 3D tissue scaffolds because cells cannot survive such an extreme printing process. An air fan can be optionally used to cool the melted polymer as it is being deposited on the print bed, in order to reduce the deforming and sagging that can occur as a result of slow solidification.

- Another type of extruder is the electrospinning-electrowriting print head (Fig. 9d), which uses electric fields to draw out a polymer solution (typically from a syringe). Given that it uses a high voltage, which would kill any cells in the ink, it is typically used to fabricate high-resolution fibrous scaffolds (which are then seeded with the cells after the manufacturing).

- Like the hot-melt extruder print heads, the filament extruder print heads (Fig. 9e) are typically used to molt a polymer to create a tissue scaffold. However, instead of melting granules or powders, a filament is pulled through a heating block via an assembly of gears and bearings. The heating block then melts the filament, and the melt is deposited via a nozzle on the print bed. The extrusion process is optionally cooled by a fan to speed up the solidification process.

- Furthermore, additional accessories, like fans, curing lights (Fig. 9f), print monitoring cameras (Fig. 9g), and other miscellaneous tools, either are typically available as separate print heads or come mounted on the ink depositing print heads. Lastly, the print bed can also come with optional heating in order to facilitate the sticking of the deposited ink to the print surface, as well as for maintaining the physiological conditions for the survival of the cells.

In our opinion, Hyrel 3D is leading the modularity trend by allowing its customers to select relatively cheap print heads from the widest range of choices (Suppl. Table S3) that we have seen: filament extrusion, syringe-based extrusion with and without temperature control, UV crosslinking, high-viscosity printing, and so forth. Furthermore, the availability of other tools, such as cameras, lasers, and engravers, allows the user to turn the bioprinter into a multitool, which
is especially lucrative for small laboratories. This modularity offers a competitive edge compared with machines from some of the other companies, which either do not provide the option to change the printer heads at all or only make a limited number of print heads available. Of course, the counter-argument may be that a machine that is focused solely on bioprinting may yield better-quality products. In any case, we see the modularity trending already because, for a relatively small price, it extends the printing capabilities of a single machine to a wide range of different technologies (even if the number of possible slots is limited to just a few).

**Microfluidic Print Heads and Scaffolds Integrated with Microfluidic “Nozzles”**

Recently, the advancement of microfluidic plumbing technologies has increasingly led to their use in synthesizing biomaterials,216 printing high-throughput assays,217 and seeding cells in engineered tissues.218 Likewise, microfluidic print heads have demonstrated great potential in replacing the traditional extrusion-based and droplet-based technologies due to numerous advantages, such as fast continuous switching and mixing of materials, high-resolution bio-ink deposition, and reducing the shear stresses experienced by the extruded cells (see the “High-End Microfluidics-Based Printers” section for more details).219,220 These new capabilities can potentially revolutionize the 3D fabrication of artificial tissues by enabling the generation of highly organized and patterned microenvironments and organoids using multicell/multimaterial bio-inks.

The industry leaders, like Aspect Biosystems and Fluicell AB, have already implemented the microfluidic printer heads in their commercially available RX1 and Biopixlar platforms, respectively. Yet, the high cost of these novel machines is still unaffordable for a typical-sized academic laboratory. Nonetheless, the components required to make the PDMS printer heads are cheap. Hence, the current high cost of the microfluidic bioprinters is likely due to their novelty. Consequently, they are expected to fall in price steadily as the technology adoption continues. Moreover, given the apparent rise of Aspect Biosystems and Fluicell AB, and the versatility of their business models (i.e., products ranging from hardware to bioengineered platforms), it is expected that these companies will continue to flourish and drive the industry standard toward making microfluidic printer heads mainstream. For these reasons, we project that microfluidic technologies will soon appear in the low-cost bioprinters as well.
Furthermore, alternative microfluidic bioprinting technologies are being developed that use the device as the photo-crosslinking print bed (as opposed to as a nozzle) (Fig. 7c). Another interesting aspect of using microfluidics to build artificial tissues and organs is microfluidic scaffolds. These devices essentially use microplumbing for in situ (i.e., inside of the scaffold) cell and fluid manipulation. For example, integrating permeant microfluidic nozzles within their channels holds the promise of effectively accomplishing both additive (e.g., cell seeding, nutrient, and drug delivery) and subtractive (e.g., undesired overgrowth and metabolic waste removal, cell biopsying, and secretion probing) manufacturing within growing artificial tissues as they are being cultured and matured. Therefore, we expect that the microfluidic and bioprinting technologies will continue to merge toward an integrated future.

However, with the use of PDMS as the print heads’ material, several disadvantages should be considered. First, it has a high hydrophobicity, which makes PDMS absorb active agents from the bio-inks. This can potentially alter the printer head’s own composition and consequently worsen its performance. Moreover, PDMS is prone to swelling and is gas permeable. These factors can contribute to the deformation of the print head’s geometry, which makes it difficult to sustain an accurate deposition of the bio-ink over time. Hence, the long-term use of the PDMS print heads is not straightforward, and the inside of their channels must be protected with a special coating to overcome these problems. Yet, even with these workarounds, it is still recommended to replace the microfluidic print heads after every 8–9 h of use, which makes the consumable costs associated with these printers significant. Therefore, some lingering challenges still need to be solved before these technologies can be fully adopted by low-cost bioprinters.

**Support-Free Multiaxial Printing**

A common feature of the low-cost 3D bioprinters surveyed in this paper is that their bio-ink deposition tools tend to be constrained to linear motion in the X, Y, and Z planes. However, such setups have limitations with respect to the type of geometries that they can produce. Additionally, they typically require the formation of support structures simply because the deposition is made in one direction (e.g., top-down). The need to produce the latter wastes material, slows down the printing time, and may require additional postprocessing to get rid of the support structure.

One possible mechanical solution to this problem is the introduction of two or three more rotational degrees of freedom, either to the motion of the deposition tool or of the sample itself (by moving its bed). This approach enables the creation of complex and intricate geometries without compromising surface quality or adding extra supports. For these reasons, the higher-end bioprinters, like the six-axis BioAssemblyBot, implement this solution. However, the machine dynamics become much more complicated than with the three-axis printing. Also, the slicing process becomes problematic because most software assumes that the layers are built up in a single direction. Nonetheless, this technology results in higher-quality prints and holds a lot of potential for in vivo applications. For example, although some devices currently used for printing into open wounds are either three-axis or handheld (which is effectively a manual six-axis configuration), several five- to six-axis robotic arms have also been introduced. Therefore, multiaxial configurations are expected to eventually appear in the low-cost bioprinters as well.

**High-Resolution Printing Using Focused Light**

Photo-crosslinking technologies are widely used in bioprinting to obtain solidified structures from the cell-laden bio-ink gels. For this purpose, many of the low-cost machines are equipped with onboard LEDs that travel together with the nozzle and expose the extruded material as it is being deposited. However, for cost-saving reasons, typically these lights are not focused on using high-fidelity optics, and the resulting printing resolution is effectively determined by the nozzle diameter.

Yet, building structures via focused light photo-crosslinking (which is typically done without the extrusion) offers significant improvements in the printing speed and resolution relative to the conventional machines that deposit the bio-ink material via nozzles. Furthermore, this approach improves product viability, given that the cells do not experience the mechanical stresses resulting from being squeezed through a small opening. However, the trade-off is that they must be present in the bed of the crosslinkable bio-ink a priori; for example, the high-end machines, like CELLINK’s Holograph X, are beginning to implement this approach of building the scaffolds via photo-crosslinking in a bed of bio-ink (that has been premixed with cells). Yet, this means that the cell positions are not manipulatable. Alternatively, the cells must be seeded into the resulting scaffold structure after it has been created via curing. This can be done through a combination of processes executed in a sequence; for example, an application from the same company first uses their Lumen X machine to photo-crosslink a scaffold and then deposits cells onto its surface using the nozzles of their BIO X printer. Furthermore, the steps can be combined in a layer-by-layer fashion to seed the cells inside of the scaffold as it is being built. However, this would require a machine to have both nozzles and high-fidelity focusing optics (possibly as different modular printing heads).

Another limitation of the focused light-based printing is that the crosslinking is typically limited to the XYZ directions, which suffers from drawbacks like those of the
three-axis extrusion. An interesting solution to this problem is the recently developed computed axial lithography (CAL), which enables synthesizing support-free geometries volumetrically via 3D photopolymerization.\textsuperscript{236,237} This is done by essentially inverting the process of tomographic reconstruction commonly implemented in CT scans. Specifically, a 3D energy dose is delivered to a photo-crosslinkable material as a set of 2D images projected from different angles, while the sample is rotated in front of a stationary light projector. This approach overcomes many limitations of conventional layer-based techniques; for example, it is able to create objects that enclose existing ones without any support structures, can print into high-viscosity fluids or even solids, is scalable to larger print volumes, and is several orders of magnitude faster, under a wider range of conditions. Additionally, the resulting structures have smoother surfaces than what can be achieved with the typical light-based 3D printers. The latter could be helpful for manufacturing optical components (e.g., tissues of the eye).

Other volumetric photopolymerization approaches, like using holographic patterning of light fields, are also being developed.\textsuperscript{238} Furthermore, like the multiaxial technologies, photo-crosslinking has found potential for in vivo applications as well.\textsuperscript{68,69} Therefore, we foresee that as new volumetric printing developments (e.g., CAL) enter the higher-end bioprinters, the existing focused light photopolymerization technologies (e.g., CELLINK’s Holograph X) will cheapen and begin to appear in the low-cost machines.

**Monitoring and Automation**

High-resolution printing requires an accurate calibration/alignment and close monitoring of the printing process. Thus, a 3D bioprinter should come with a monitoring module such as a high-resolution camera, sensors, and probes. However, per Supplemental Table S1, this feature is not present in many of the low-cost systems, except for Brinter’s 3D BioPrinter, FELIX’s BioPrinter, Axolotl Biosystems’ AXO A3, CELLINK’s BIO X, ROKIT HEALTHCARE’s DR. INVIO 4D, and Fujifilm Dimatix’s DMP-2850. These models are integrated with cameras for accurate alignment, droplet and/or pattern inspection, and printing process monitoring. Furthermore, some of the other low-cost models, like Hyrel 3D’s and Axolotl Biosystems’ printers, sell digital microscopes/cameras that can be mounted in modular slots for close-up inspection and observation. Finally, many of the high-end models utilize the abovementioned observation and sensing hardware in order to automate the calibration and alignment processes. This results in more consistent, higher-quality prints. Therefore, we anticipate that the low-cost printers will soon adopt many of these features, especially considering that it is relatively cheap for them to do so.

**Sterilization**

Whether or not a laminar-flow chamber with a HEPA filter is needed for a low-cost bioprinter is debatable. On the one hand, having a BSC built in provides users with a higher level of flexibility. On the other hand, it significantly increases the cost and the dimension of the unit without improving the printing quality. Also, since most bioengineering labs are equipped with BSCs that are large enough to fit small machines, printers without a built-in BSC may be preferred as a cost-saving measure. Overall, our observation has been that the machines on the market either have a footprint small enough to fit in a BSC or come with onboard sterilization. We anticipate that this trend will remain as is.

**Open-Source Do It Yourself (DIY) Community**

Given the recent popularity of bioprinting, there is a push toward making the technology universally available. For example, low-cost methods for modifying a standard desktop 3D printer with a bioprinter head have recently been published.\textsuperscript{239,240} Likewise, Aleph Objects’ Lulzbot open-source business model is a step in the right direction. Furthermore, some community-driven open resources are also becoming available.\textsuperscript{241} However, they do not yet appear to be as well developed as their analogs in other disciplines (e.g., OpenSpim website for DIY microscopy).\textsuperscript{242} Therefore, it is expected that this area of low-cost bioprinting will grow in the future.

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