pISSN 1738-2696 · eISSN 2212-5469
https://doi.org/10.1007/s13770-016-0148-1
SPECIAL ISSUE – REVIEW ARTICLE

TERM

Three-Dimensional Bio-Printing Equipment Technologies for Tissue Engineering and Regenerative Medicine

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Three-Dimensional (3D) printing technologies have been widely used in the medical sector for the production of medical assistance equipment and surgical guides, particularly 3D bio-printing that combines 3D printing technology with biocompatible materials and cells in field of tissue engineering and regenerative medicine. These additive manufacturing technologies can make patient-made production from medical image data. Thus, the application of 3D bio-printers with biocompatible materials has been increasing. Currently, 3D bio-printing technology is in the early stages of research and development but it has great potential in the fields of tissue and organ regeneration. The present paper discusses the history and types of 3D printers, the classification of 3D bio-printers, and the technology used to manufacture artificial tissues and organs.
Tissue Eng Regen Med 2016;13(6):663-676

Key Words: 3D printer; 3D bio-printer; Inkjet; Extrusion; Laser assisted; Electrospinning

HISTORY OF THE 3D PRINTER

A three-dimensional (3D) printer is one of equipment that uses various methods to produce objects through the layer by layer addition of materials. As it allows a high degree of freedom, items of various shapes and sizes can be produced without wasting resources. It can also be applied in a variety of fields depending on the materials used.

The 3D printer was first introduced in 1981 in a technical report by Kodama [1] of the Nagoya Municipal Industrial Research Institute. The described technology produced an object by curing a liquid photo-curable resin using laser ultraviolet (UV) light. Research was conducted on a method for layering liquid photo-curable resin in a water tank using UV light and a mask.

The first 3D printer was made in 1984 at 3D Systems by Hull [2], who developed 3D printing technology based on stereolithography apparatus (SLA). This was a layered curing method in which sections of models were exposed to UV light in the same manner as the technology used by Hideo Kodama. Hull founded 3D Systems, developed 3D printers, and introduced them to the market for the first time in 1988. He also developed a stereolithography file, which is a standard CAD model file format used in current 3D printers, and began the commercialization of 3D printers in earnest.

In 1986, Deckard [3] developed a 3D printer with a selective laser sintering (SLS) method by small particle powders using a laser, for which a patent was acquired in 1989. This technology also was called direct metal laser sintering; Deckard founded the Desk Top Manufacturing (DTM) Corporation, thereby making commercialization successful. DTM merged with and was then acquired by 3D Systems in 2001.

In 1987, Hornbeck [4] from Texas Instruments in the USA developed a digital light processing (DLP) technology, which uses a digital mirror device (DMD) in which a product can be fabricated using a repeated curing method using light that is projected from the DLP unit onto a liquid photo-curable resin.

In 1988, the Helisys Company in the USA acquired a patent for the laminated object manufacturing (LOM) method [5].

In 1992, Crump [6] developed and applied for a patent on a fused deposition modeling (FDM) method, in which thermoplastics were melted and layered. He then founded the Stratasys Company and launched a 3D printer into the market using FDM.

Received: October 18, 2016
Revised: November 15, 2016
Accepted: November 17, 2016
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In 1991, Brother Kogyo Kabushiki Kaisha in Japan acquired a patent for a jetted photopolymer [7], and 3D Systems acquired a patent related to a multi-jet modeling (MJM) method in 1992 [8].

In 1993, the Massachusetts Institute of Technology first developed and applied for patent protection on powder bed and inkjet head 3D printing, which was a new technology involving a three-dimensional printing (3DP) technique that was similar to the inkjet printer [9]. The Z Corporation was founded based on this technology and the company applied for a patent on 3DP in 1996 [10]. The Z Corporation then merged with and was eventually acquired by 3D Systems in 2012.

Since then, a variety of methods have been introduced and many 3D printers have been launched into the market. However, due to their cost, 3D printers were only used in specialized fields until 2005 when commercialization began.

Since 2005, Adrian Bowyer has been conducting an open source project called Replication Rapid Prototyping (RepRap) using a fused filament fabrication (FFF) method, which is similar to FDM. The patent for the SLA method expired in 2006, the patent for the FDM method expired in 2009, and the patent for the SLS method expired in 2014.

As the patent for the FDM method, which does not require expensive equipment and uses inexpensive raw materials, has expired, the hardware and software needed to manufacture with FFF 3D printers (the FDM method) can now be unrestrictedly disclosed through the Reprap project. Accordingly, a number of companies have attempted renovated models using the disclosed patents so that an increasing number of inexpensive entry level printers have been launched. Thus, 3D printers can now be manufactured economically.

CLASSIFICATION OF 3D PRINTERS

The first technical standards on 3D printers were described by the ASTM in the USA. The standards were defined by the International F42 Committee in 2009 and are also used by the International Organization for Standardization (ISO) (Table 1) [11]. The 3D printing method can divide into subtractive manufacturing and additive manufacturing (AM). Subtractive manufacturing makes objects by removing materials such as CNC milling, drilling, grinding, and carving and AM builds 3D objects by layer-upon-layer of materials. According to ISO/ASTM 52900, there are seven types of AM technologies: binder jetting, directed energy deposition, material extrusion, material jetting, powder bed fusion, sheet lamination, and vat photopolymerization (Fig. 1) [12].

Binder jetting

Liquid glue is sprayed through nozzles in the inkjet head, binding the powdered materials. A typical binder jetting method is color jet printing (CJP).

CJP employs the same principle as an inkjet printer to spray colored materials from nozzles in the printer head, layer by layer, and then hardens the powders by spraying a binder onto them. This method can produce various colors, and the surrounding powders support the object. However, the powder support is weak and removing the powders from the surface in post-processing procedures is cumbersome [13-16]. 3D Systems [17] is one of the companies that used this technique.

Directed energy deposition

This method sinters powdered materials using an energy

Table 1. Standard terminology for additive manufacturing technologies [11]

Process categories	Method	Technology
Binder jetting	An additive manufacturing process in which a liquid bonding agent is selectively deposited to join powder materials	CJP (color jet printing)
Directed energy deposition	An additive manufacturing process in which focused thermal energy is used to fuse materials by melting as they are being deposited	DMT (laser-aided direct metal tooling)
Material extrusion	An additive manufacturing process in which material is selectively dispensed through a nozzle or orifice	FDM (fused deposition modeling)
Material jetting	An additive manufacturing process in which droplets of build material are selectively deposited	Polyjet (photopolymer jetting) MJM (multi jet modeling)
Powder bed fusion	An additive manufacturing process in which thermal energy selectively fuses regions of a powder bed	SLS (selective laser sintering)
Sheet lamination	An additive manufacturing process in which sheets of material are bonded to form an object	LoM (laminated object manufacturing)
Vat photopolymerization	An additive manufacturing process in which liquid photopolymer in a vat is selectively cured by lightactivated polymerization	SLA (stereo lithography apparatus) DLP (digital light processing)

Adapted from: https://www.iso.org/obp/ui/#iso:std:iso-astm:52900:ed-1:v1:en

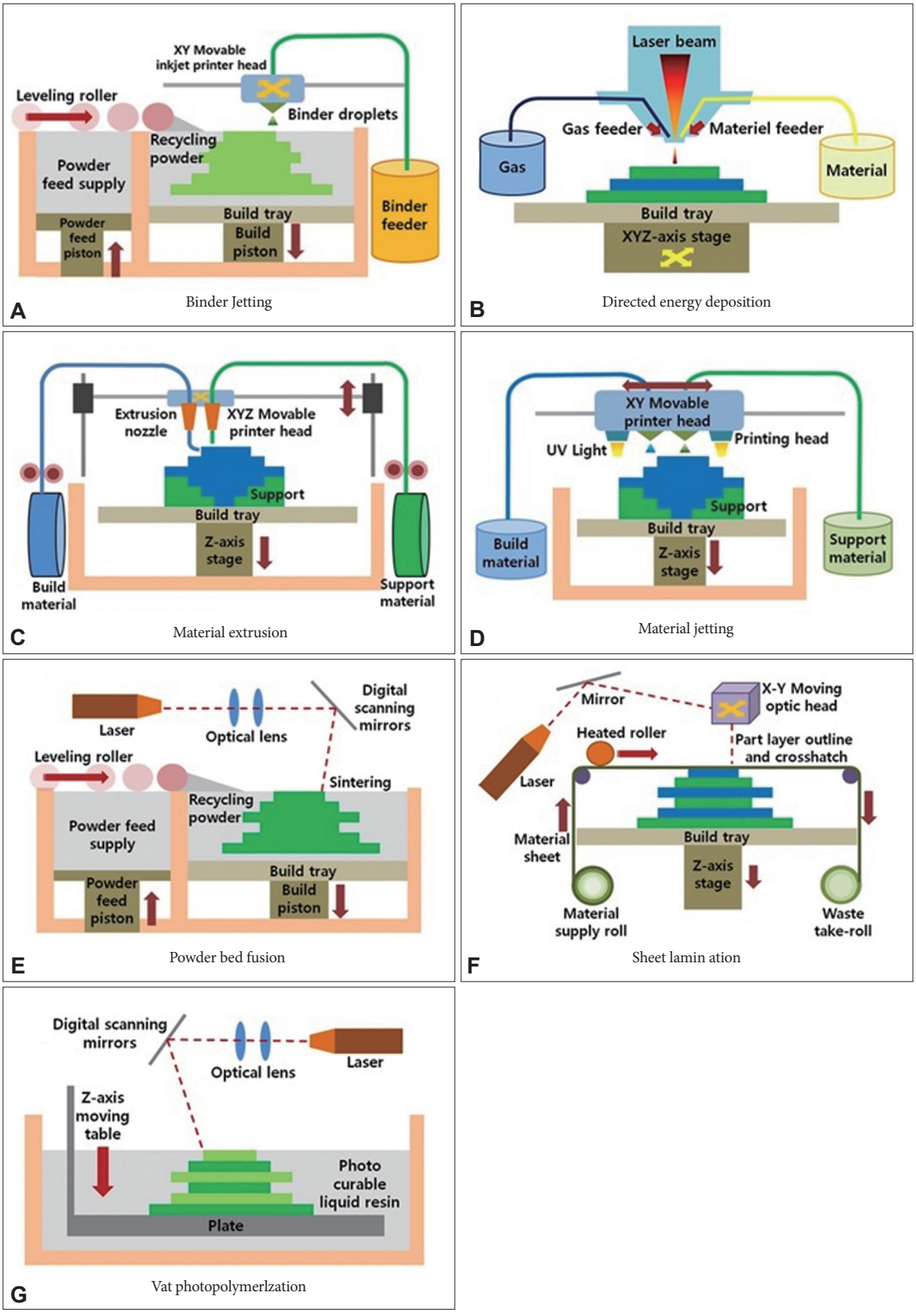

Figure 1. Components of additive manufacturing technologies. (A) Binder jetting, (B) directed energy deposition, (C) material extrusion, (D) material jetting, (E) powder bed fusion, (F) sheet lamination and (G) vat photopolymerization. UV: ultraviolet.

source such as a laser. Directed energy deposition melts metal powders using a high-powered laser beam while depositing powders on a molding plate. It can melt materials completely and layer the materials on existing structures [18-21]. It has the advantage of metal product production and the disadvantage of difficult post-processing of the melted residuals attached to the surrounding structure. Insstek [22] and TRUMPF [23] are two of the companies that use this technique.

Material extrusion

In this method, filaments or pellet materials are melted and the material is extruded through a nozzle via the application of pressure.

The generally known FDM method is a material extrusion method. It is the trademark method of Stratasys [24], who has acquired the patent. As such, it is known as the FFF method in the RepRap open source project.

In the FDM method, thread-like thermoplastics are passed through heated nozzles to melt them and the melted filaments are laid layer upon layer. This method has the disadvantages of a slow molding speed and weak bonding because only the edges are melted. However, it is a relatively inexpensive and simple mechanism and the patent expired in 2009. Based on these advantages, a large number of 3D printers employ the FDM method [25-29].

Material jetting

In this method, the materials are sprayed while one or more heads are moved. Photopolymer jetting (polyjet) and MJM are two representative material jetting methods. The polyjet method is a combination of the photocurable and inkjet methods in which materials are sprayed from hundreds of fine nozzles located in the printer head while they are simultaneously cured by UV light. Since the layers are thin, the modelling is accurate and post-processing is unnecessary, however, it is an expensive method [30-31]. Stratasys [24] uses this method.

The MJM method sprays acrylic photopolymer as the main material and wax as the supporting material during simultaneous curing with UV light. This is similar to the polyjet method but it can produce multiple materials with different properties. Since this is a high-precision method, no post-processing is needed and the transparency of the acrylic photopolymer can be controlled. However, the weakness of the final product and the cost of the method represent the method's disadvantages [32,33]. 3D Systems uses the MJM method [17].

Powder bed fusion

This is an AM technology in which the preferred shape can be layered via powdered materials using a laser. SLS is a powder bed fusion method in which fine metal, plastic, ceramic, or glass powders are melted via the heat from a laser. It is similar to the SLA method in which a single layer is pulled down after a layer is molded and the next layer is molded using a laser. As the molding preparations are covered with powder, no support is needed and the items produced using this method are strong. However, it has the disadvantage of a cumbersome post-processing procedure to remove the residual powder. 3D Systems [17] uses this method for direct metal printing, and EOS [34] uses it for DMLS [35-41].

Sheet lamination

In this method, paper thin plates materials, such as strawboard or rolled PVC laminate sheets, are cut with a precise cutter, such as a knife edge or a CO_2 laser, and then bonded with heat to produce a shape. One of the typical methods is LOM developed by Helisys (currently, Cubic Technology, Phanom Penh, Cambodia) [42]. It is an additive technology using glue or heat to layer thin film-shape materials (paper, plastic, or metal laminates) layer by layer. Its manufacturing cost is relatively low and timber-looking products can be produced. However, products have the disadvantage of inflexibility due to their low durability [43,44]. Mcor Technologies [45] uses this method.

Vat photopolymerization process

SLA and DLP methods are two vat photopolymerization process methods in which liquid photo-curable resin is selectively cure using UV or light energy.

The SLA method is the world's first 3D printing technology in which liquid photo-curable resin in a vat is hardened using a laser. Once a layer has been hardened, it is pulled down and the next layer is hardened with the laser. The SLA method has the advantage of precise molding; however, the support must be removed after molding, only curable materials can be used, and the finished products have poor durability [46-48]. 3D Systems [17] and Formlabs [49] in the USA, Shanghai Union Technology [50] in China, CMET [51] in Japan, and DWS [52] in Italy are some of the companies that use this technology.

The DLP method employs the same principle of beam projection as DMD. It is an additive technology in which 3D CAD data is sliced layer by layer in a liquid photo-curable resin via a light projector. It is similar to SLA in terms of the layer by layer liquid photo-curable resin but it has a relatively faster speed because an entire layer section can be irradiated at once, no additional support materials are needed, and smooth and precise molding can be achieved. However, it is generally expensive, produces small moldings, and the available raw materials and colors are limited [53-56]. EnvisionTEC in Germany [57] uses this method.

HISTORY OF 3D BIO-PRINTERS

Currently, most organs and tissues used for transplantation are taken from human donors; however, the numbers of suitable and/or compatible donated organs and tissues are not sufficient to meet the demand. Furthermore, organ and tissue are vulnerable to auto-immune reactions after transplantation and immunosuppressive drugs need to be administered. In order to solve such problems, doctors and scientists have started to conduct research through a new technology known as tissue engineering [58]. A number of studies have combined tissue engineering and 3D printing technologies.

3D bio-printing refers to the fabrication of tissues and organs in three-dimensional structures by layering tissue specific cells and biomaterials [59].

In 1993, tissue engineering was introduced by Langer and Vacanti [58]. Since that time, many studies have been conducted.

Tissue engineering using scaffold has several advantages such as a mechanical support and specific instructive environment for cellular function.

A method utilizing 3D printing can apply imaging technology such as computed tomography (CT) or magnetic resonance imaging (MRI) to manufacture complex structures of custom-tailored shapes and sizes as well as internal shapes, and pores can be controlled to adjust the diffusion of oxygen, nutrients, and waste of cells, thereby promoting cell attachment, proliferation, and differentiation [59-65].

Since the early 2000s, a variety of biocompatible and biodegradable materials have been used to manufacture scaffolds using 3D bio-printers and a number of studies on the generation and regeneration of organs and tissues have also been conducted [64,65]. Some typical examples are described below.

Landers and Mülhaupt [60] removed milling machine heads and mount pneumatic dispensers to manufacture various patterns scaffolds. In 2002, a number of studies were conducted by Envision TEC using extrusion method of 3D bio-printer [61-65]. In 2005, scaffolds were manufactured using 3D bioplotting™ equipment and in 2014, 3D-BIOPLOTTER® (Envision TEC, Gladbeck, Germany) was commercialized [57]. In 2002, Zein et al. [29] manufactured a honeycomb-shaped scaffold applying FDM extrusion technology using a biodegradable material polycaprolactone (PCL). In 2003, Pfister et al. [66] manufactured scaffolds using 3D printing and 3D bioplotting methods, respectively, and compared them. In 2007, a team led by Professor W. Sun manufactured a scaffold using PCL and hydroxyapatite (HA) [67].

In addition to scaffold manufacturing methods using 3D bioprinters, other studies on printing with factors that help cell activation or tissue differentiation or on the direct printing of cells have also been undertaken [68-70].

In 1994, Klebe et al. [71] used a commercialized HP Thinkjet printer to print fibronectin and then seed SV-T2 (SV40-transformed BALB-3T3 cell line) cells. In 2004, Roth et al. [72] of Clemson University successfully printed cells in his laboratory by filling a Canon inkjet printer cartridge with collagen, and demonstrated the use of Canon and HP printers to print collagen and bacteria in 2003 [73]. Based on these successes, research on printing ovary cells was conducted [74] and the first patent for inkjet printing of viable cells was applied for [75].

In 2003, Mironov et al. [76] fabricated tube-shaped tissues such as blood vessels by printing alternate layers of cell aggregates and gel.

In 2004, Forgacs et al. [77] applied for a patent titled "self-assembling cell aggregates and methods of making engineered tissue using the same," which was a bio-printing-related patent [77] based on this work, Organovo was founded in 2005. In 2009, Norotte et al. [78] manufactured cells of a certain unit structure size (multicellular spheroid), printed blood vessels without scaffolds, and sold 200–500 μm thick printed liver cells, commercializing 3D bio-printing technology for the first time [79].

Recently, a decellularized extracellular matrix (dECM) bioink is used for 3D bioprining [80]. In 2014, Pati et al. [80] made a scaffold using a cell-laden dECM bioink isolated from adipose and cartilage and confirmed high cell viability and functionality.

In addition to fabricating scaffolds or direct printing of cells, 3D printers have been used with various methods in the medical field.

Around 2000, commercialization of high-precision 3D printers began and ever since, 3D printing technology has been applied to biomaterials to be utilized both directly and indirectly in the medical field. As computer design technology and engineering technology have advanced, 3D printing technology has improved and has been utilized in prototype production mainly by taking advantage of immediate production using digital data. Moreover, there have been many attempts at fabrication of physical assistance equipment, rehabilitation devices, visualization for medical environment, and medical tools [81-83].

CLASSIFICATION OF 3D BIO-PRINTERS

Bio-printing can be divided into three modes: inkjet mode, by making materials into ink droplets; extrusion mode, by pushing materials with pressure; and laser-assisted mode, by dropping materials using a laser (Fig. 2) [84]. A summary of these techniques is presented in Table 2.

Inkjet

Inkjet-based methods employ cells or biomaterials instead of

the ink used in existing commercial inkjet printers, and utilize a moving stage instead of paper. Inkjet cell printing can be divided into the thermal heater method [74] and the piezoelectric actuator method [85-87].

The thermal heater method is known as the bubble-jet method developed by HP and Canon, in which bubble nucleation is generated instantaneously at the nozzle due to heat and bubbles are created to turn the materials into ink droplets, which are then pushed out of the nozzle. For commercial inkjet printers, a temperature of 200 to 300°C is applied to the nozzles, which will deform or destroy polymers or cells [88]. To prevent this, a temperature of 40–45°C is applied to melt biomaterials in order to make ink droplets [89].

The piezoelectric actuator method is a method for printing biomaterials by applying a voltage to the piezoelectric elements. Ink droplets are created by the physical force generated during voltage application to the piezoelectric elements rather than the application of temperature to the nozzle. This method can control the size of droplets. However, the cells are affected somewhat by the physical impact. The inkjet method is inexpensive and various materials can be employed. In addition, the dropping speed is fast, resulting in a short fabricating time. However, the products fabricated using this method is not very weak and the layers cannot be stacked very high. It also has the disadvantages of possible denaturalization of the biomaterials and inconsistent ink droplets.

In 2005, a team led by Professor Thomas Boland printed ovary cells using the inkjet method 2. In 2009, Cui and Boland [90] fabricated a structure similar to blood vessels using an inkjet printer. He fabricated a 10 μm diameter blood vessel structure using human microvascular endothelial cells.

Extrusion

Extrusion-based methods print cell laden biomaterials using mechanical force via screws, pistons, or pneumatics. This is the most widely used commercial method.

Extrusion methods are also divided into two types: pneumatic [91-93] and mechanical [94-98] methods. Pneumatic methods extrude materials using pressure. A constant pressure should be maintained, but pneumatics limit the ability to control pressure. One way to mechanically control displacement is to directly extrude materials using pistons, which are easy to control.

Since extrusion methods can employ more viscous materials than inkjet methods, multiple biomaterials and cell types can be used simultaneously. These methods are also most common method for bio-printing. However, nozzles frequently become

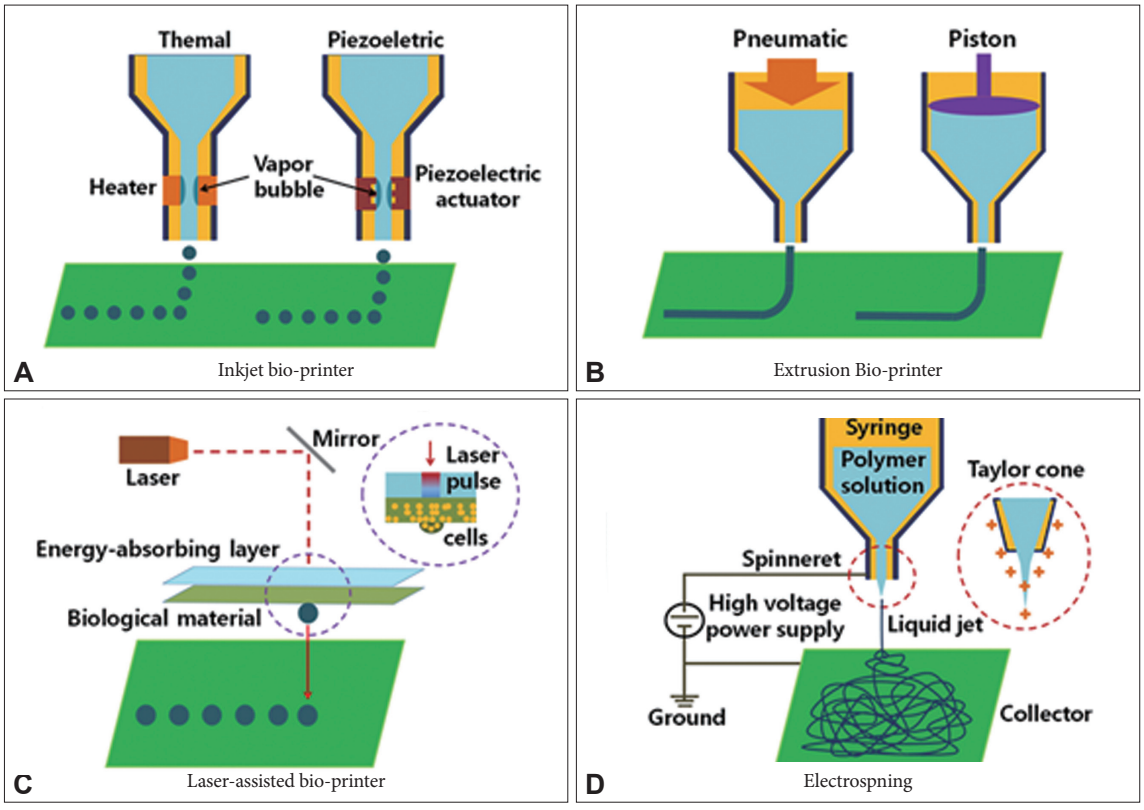

Figure 2. Classification of bio-printer. (A) Inkjet bio-printer, (B) extrusion bio-printer, (C) laser assisted bio-printer and (D) electrospinning.

Table 2. Comparison of the inkjet bio-printer, extrusion bio-printer, laser-assisted bio-printer, and electrospinning

	Inkjet	Extrusion	Laser assisted	Electrospinning
Resolution	Medium	Medium	Low	High
Materials	Natural polymer, synthetic polymer+cell	Natural polymer, synthetic polymer+cell	Cell in media	Natural polymer, synthetic polymer
Print speed	Fast	Slow	Medium	Fast
Cell viability	Medium	Medium-high	High	-
Printer cost	Low-medium	Low-medium-high	High	Medium-high
Advantages	Versatile low cost	Multiple compositions	High accuracy single cell manipulation	Nano-size pores
Disadvantages	Low viscosity prevents build up in 3D	Low accuracy limited biomaterial used	Low viscosity prevents build up in 3D	Difficulty in shape control
References	75, 85–88	92–99	100–106	107–109

blocked and extrusion methods are poor structural stability.

In 2009, Lee et al. [99] used an extrusion method to fabricate multi-layered skin tissue using fibroblasts and keratinocytes. In 2009, Mironov et al. [93] printed cell spheroids using a 3D dispensing laboratory bio-printer called LBP. In 2009, El-Ayoubi et al. [98] manufactured scaffolds using bioplotting, which is an extrusion method, from a biodegradable material called poly-L-Lactide (PLLA). The survival rate of the fabricated cells was verified by attaching chondrocytes to a PLLA scaffold with different porosities.

Laser assisted methods

Laser-assisted methods create structures using a laser and various materials. Such methods involve the use of an energy-absorbing layer that prevents cells, and biological material that helps the growth of cells, from being directly exposed to the laser. Bubbles are formed in biological materials located under the energy-absorbing layer, and the laser stimulates the printing by dropping the materials containing cells [99-105].

A laser assisted method is highly precise and as nozzles are not required, blocking does not occur. It can also control a single cell. However, such method's drawback is that cells can be damaged and difficulties can be encountered in high 3D layering.

In 1999, Odde and Renn [103] printed cells using a laser in which only the small arrays were used; survival of the cells after printing was verified.

Electrospinning

An electrospinning method does not print cells directly but is a method for fabricating a scaffold using cytocompatibility biomaterials. A scaffold manufactured via electrospinning is produced from nano-type fibers, which are suitable for the structural characteristics of extracellular matrix (ECM) [106-108].

This method uses fiber formed when electrostatic force is applied to a polymer solution or melting body. It mainly consists of three devices: a power supply, a spinneret, and a collector. A solution is suspended at the end of vertically positioned capillary, which is hung and maintained via the equilibrium between gravity and surface tension. Upon the application of high voltage, the solution is changed into a Taylor cone shape due to mutual electrostatic repulsion between surface charges and a coulomb force is applied to the external electric field thereby forming a tiny diameter jet stream due to the Taylor cone effect [109]. Immediately, elongation and evaporation of the solvents occur simultaneously as the solution is directed to the grounded collector and the microfibers are randomly arranged [110].

The above electrospinning method manufactures a nano-size pore thereby having advantages that are suitable for the anchorage, migration, and proliferation of cells. However, it has the drawback of difficulties in shape control.

In particular, as it is not suitable to utilize tissues in which cells and ECM are aligned with each other, such as in musculature, without modification, other manufacturing and electrospinning methods are used in combination [111,112].

In 2003, Yoshimoto et al. [113] manufactured a PCL scaffold using an electrospinning method. He checked cell differentiation by seeding mesenchymal stem cells to the manufactured scaffold.

In 2008, Park et al. [111] manufactured a PCL scaffold that had both nanofibers and microfibers using both electrospinning and extrusion methods.

APPLICATIONS OF 3D BIO-PRINTER

Medical equipment

The market for 3D bio-printing has grown continuously since its inception. This means there are many common areas where bio-printing can contribute to meeting the requirements for medical equipment. Medical equipment is characterized by its relatively small size, expensive products, and customization

Table 3. Overview of 3D bio-printing technologies for generation of tissue and organ

Bio-printing technique	Building materials	Cell types	Applications	Printing conditions	Ref.
Powder bed fusion	HA	MC3T3-E1	Bone	Sintering: 2 h Temperature: 1300°C	[128]
Extrusion	PCL	MC3T3-E1	Bone	Heating dispenser: 80°C Air pressure: 300 kPa	[131]
Extrusion	PEGT/PBT	Bovine articular chondrocytes, human articular chondrocytes	Cartilage	Temperature: 180, 200°C Applide force: 1.5, 2.0 kN	[135]
Extrusion	Nanofibrillated cellulose (NFC), Alginate	Human nasoseptal chondrocytes	Cartilage	Printer head: microvalve dispenser Valve opening time: 400–1200 μs Dispensing pressure: 20–60 kPa	[133]
Extrusion	Collagen hydrogel	Fibrochondrocyte	Cartilage	Baseplate temperature: 37°C	[134]
Extrusion	Hydrogel	Multicellular spheroid: human umbilical vein smooth muscle cells (HUVSMCs), human skin fibroblasts (HSFs)	Blood vessel	Scaffold-free tissue fabrication technology	[78]
Electrospinning	Collagen type I, elastin, poly(D,L-lactide-coglycolide) (PLGA)	Bovine endothelial cells, bovine smooth muscle cells	Blood vessel	Voltage potential: 25 kV Distance: 15 cm Rotation rate: 50 rpm	[136]
Electrospinning, extrusion	PCL, chitosan (CTS)	-	Blood vessel	-	[140]
Inkjet	-	Fibroblasts, keratinocytes	Skin	HP deskjet 640c series inkjet printer modified	[145]
Extrusion	Alginate hydrogel	Chondrocyte	Ear	-	[146]
Inkjet	Collagen, polyglycolic acid	Urothelial, muscle cells	Bladder	-	[149]
SLS (selective laser sintering)	PCL, HA	-	Trachea (personalized medical devices)	-	[150]

HA: hydroxyapatite, PCL: polycaprolactone

needed to cater to personal differences depending on the patient's physical structure; all of these characteristics make the application of 3D bio-printing technology appropriate in the medical equipment field.

A 3D printer can not only save time and cost by reducing the manufacturing process, but it also contributes to the customization of products as it can reflect the physical structures of individual patients using a scanner. It is also advantageous in terms of fast modification and change speeds.

Using such advantages, a hearing aid is a good example of a widely used medical assistive device. With a 3D printer, a hearing aid can be manufactured to fit the shape of a patient's ears using 3D scanning and the implementation of a precise model. It can reduce the manufacturing process thereby saving cost and time.

3D printing is also used in the fabrication of prosthetic legs and hands, which can be manufactured by taking different body shapes and patient preference into consideration, in contrast to monolithic and uniform shapes [114,115].

3D printing is increasingly being used in surgical applications. As the types of materials that can be used in 3D bio-printing are increasing, and as advancements are being made in CT and MRI imaging technologies, the precision of 3D printing has also been increasing. For example, surgical guides that can account for the physical structure of the patient can be manufactured to increase surgical success rates [116].

This is accomplished by helping surgeons to identify the size or location of an organ using a phantom model of the patient, which can help surgeons to prepare their operation plan, practice the operation process, and reduce unforeseeable risks. Such phantoms can also be used by medical students to practice their skills without using cadavers.

In 2002, the University of California Los Angeles (UCLA) Mattel Children's Hospital manufactured a phantom utilizing 3D printing technology to assist in the separation of Siamese twins. Although a similar separation operation previously took about 100 hours, the 2002 operation took only 22 hours and was completed successfully because of practice on a model fabricated with a 3D printer prior to the operation [117].

Furthermore, models made using 3D printers can be used as surgical guides at operating room. Such guides can help with the accurate site of surgical tools at incision and transfixion locations [83,118-122]. Surgical guides previously manually manufactured by humans, took a long time to make and presented difficulties in the manufacture of accurate shapes that corresponded to the patient's physical and anatomical shape. It is important to use the correct surgical guide for different surgical areas, particularly for operations that involve blood vessels.

Tissue and organ regeneration

A number of studies on artificial tissues and organs using 3D bio-printing technology have been undertaken not only for temporary relief and maintaining function, which have been performed previously, but also for the purpose of tissue repair and regeneration [123] (Table 3). A growth factor that can augment cell differentiation can be printed together with scaffold or biomaterials and cells can be printed directly.

Bone

Among the regeneration of tissues, the most expected and fastest area of application of 3D printers is with bone. Since bone consists of a simpler formation than other tissues and the defect zone is mostly non-uniform shaped, a number of studies have been conducted to fabricate bone using 3D printers [124-131]. Because bone characteristically has to withstand great loads, scaffolds made from ceramic and biodegradable polymers have been manufactured for bone regeneration applications.

A research team led by W. D. Kim fabricated a biodegradable PCL scaffold using an extrusion method for bone tissue engineering [131,131].

Cartilage

To regenerate cartilage tissue, a scaffold is needed to grow chondrocytes or stem cells. For this purpose, a scaffold was fabricated using polymer compounds or natural polymers. The fabrication employed a 3D bio-printer extrusion method. Some of the representative models are regenHU (Villaz-St-Pierre, Switzerland), Fab@Home, and EnvisionTEC (Gladbeck, Germany) [132-135].

Blood vessel

Blood vessel must have elasticity and durability that can endure repeated expansion and contraction. Artificial blood vessels have been developed using polymer compounds. However, due to problems such as thrombosis and stenosis, studies on the use of biodegradable polymers have been conducted [136,137]. A scaffold manufactured via electrospinning using various methods has the advantage of having the characteristics of ECM analogs due to its porosity; however, its pore size is tiny and connectivity is low [138-140].

Norotte et al. [78] produced the vascular structure of 300–500 um using extrusion method after making the multicellular spheroids with human umbilical vein smooth muscle cells and human skin fibroblasts. Marga et al. [141] manufactured the vessel structure using NovoGen MMX Bioprinter™ of Organovo (San Diego, CA, USA) with aortic smooth muscle cells (HASMCs), human aortic endothelial cells and human dermal fibroblasts.

Skin

Skin tissue damaged due to burns or injuries can be treated using an autograft of the patient's own skin, a homograft or allograft, which involves the transplantation of donor skin, or a heterograft or xenograft, which involves the transplantation of animal skin. However, the above methods have drawbacks due to immune rejection. To overcome this limitation, studies have been conducted on the fabrication of artificial skin [142-144] as well as skin regeneration using 3D bio-printers instead of artificial skin.

The Wake Forest Institute for Regenerative Medicine developed a direct printing technology for skin cells using inkjet technology. Effective treatment was achieved via printing on the skin wounds of a pig using fibroblasts and keratinocytes [145].

Ear

An artificial ear was fabricated by a joint research team from Princeton University and Johns Hopkins University using a syringe extrusion 3D printer. The shape of the ear was printed using chondrocyte-containing alginate hydrogel. The device used was a Fab@Home 3D printer. After printing, a coil antenna was embedded to detect wireless signals using silver nanoparticles (AgNP). Sound waves were received through the antenna [146].

Liver

An artificial liver was manufactured by the Organovo Company through the development of a liver cell cartridge in a 3D printer.

To do this, an extrusion method was employed using the Novogen device. The artificial liver consisted of a number of cell types including human liver cells. It was manufactured in 20 layers and had the same cell density as that of native tissue. The new liver tissue functioned like a real liver for 40 days it produced albumin, transferrin, and fibrinogen. Such manufactured liver tissue can be expected to be used in medical research, such as the testing of new drugs [79,147].

Bladder

Anthony Atala of the Wake Forest Institute for Regenerative Medicine regenerated a bladder for a patient with a 3D bioprinter using an extrusion method [148,149].

Half of the damaged human bladder was cut, normal cells were collected, and the cells were cultured for 7 to 10 days to yield a sufficient number of cells. The cultured cells were injected into a bladder-shaped scaffold manufactured using collagen. Then, the form was cultured in a bioreactor for about seven weeks and sutured to the other half of the patient's bladder to restore some of its function.

Trachea

The University of Michigan fabricated a lung splint using bioabsorbable powder material and a powder bed fusion method and transplanted it to the bronchi of an 18-month old child who suffered from shortness of breath. A model that was matched to the child's airway structure was fabricated and a splint was manufactured using 3D printing technology. The splint was fabricated using a 3D printer (EOS P 100) via the SLS method using 96% PCL and 4% HA. The splint wrapped around the external sides of the airways and ensured a breathing space, resulting in improvement to the child's respiration [150].

CONCLUSION

A large number of studies on 3D bio-printing technology have been conducted in tissue engineering and regenerative medicine. It has been widely applied in the fabrication of medical equipment such as medical assistive devices and surgical guides. Although in the early stages, this technology has opened new possibilities for the regeneration of tissues and organs.

The demand for artificial organs is steadily increasing because of an aging society which is a product of medical advancements and improvements. The supply of human organs cannot keep pace with the demand for them. This problem can be resolved through the use 3D bio-printing technology, which has proved the potential but still has a long way to go. Although many challenges must still be overcome in organ printing, a variety of alternatives have already been proposed by a number of researchers.

Medical technology and organ regeneration using 3D printing technology is expected to improve the quality of life for our aging society.

Acknowledgements

This work was supported by the Industrial Strategic Technology Development Program (Grant no. 10053020) funded by the Ministry of Knowledge Economy (MKE, Korea).

Conflicts of Interest

The authors have no financial conflicts of interest.

Ethical Statement

There are no animal experiments carried out for this article.

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