

Review Article

Three-Dimensional Printing and its Future in Medical World

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Abstract

Since the time of its inception, three-dimensional (3D) printing has not only fascinated the researchers but also health professionals. Although the process is exciting, it involves meticulous coordination and selection process to achieve a desirable product. This review article discusses about the history of evolution of 3D printers, their current application, and future trends. Emphasis has also been laid to recognize the best suitable product and ways to prevent its misuse.

Keywords: Three-dimensional printer, Material testing, Medical application, Rapid prototyping, Regulations



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Introduction

The term three-dimensional (3D) printing was initially used to describe a process to deposit a binder material by inkjet printer heads, layer by layer, onto a powder bed. It was developed mainly as a rapid and cheaper alternative to industrial prototyping process. It has become the first choice of industry for prototyping and is known as rapid prototyping (RP).^[1] Over the years, people have realized the immense potential of this technology and are being termed as third, fourth, and fifth industrial revolution by various opinion makers.^[2-6] The use of 3D printing technology in medicine is proliferating rapidly and is being extensively used in research, teaching, prosthetics, and orthotics for customized implants, presurgery 3D modeling, and tissue printing.^[3,7-10]

History

The first mention of 3D printing RP is as an application filed for patent in 1980 in Japan by Dr. Kodama. He did not subsequently file the full patent specifications required and therefore was not given the patent. The first patent was given to Chuck Hull in 1986 for stereolithography apparatus (SLA).^[11] He is the cofounder of 3D systems corporation. In 1989, Carl Deckard was issued a patent in the US for the selective laser sintering (SLS) another RP process.^[12-14]

Furthermore, in 1989, Scott Crump, a cofounder of Stratasys Inc., was issued a patent for fused deposition modeling (FDM) another technology for 3D printing.^[15] In fact, FDM has become the most popular technology in low-cost 3D printers, worldwide.^[15]

Additive Process

To understand what is 3D printing and how is it different from traditional printing, one needs to understand two concepts, two-dimensional printing by desktop printers and carving or sculptures.^[16] 3D printing is most commonly done by printheads (ink) similar to the office or home desktop printers, and hence, the technology gained the popular name of 3D printing.^[2-6,8-10] The difference is that, instead of ink, the printheads dispense various materials such as plastics, metals, and wood powder. It is more appropriate to compare it with carving or sculptures. Conventionally, sculpture is made by the artist with a visual image in mind and carving or chiseling the stone slowly reducing the complete stone into the end product. The chiseled stone is mostly wasted, famous example is construction of Taj Mahal. This type of carving whether in stone, wood, etc., is called subtractive process because the original starting material is subtracted to produce the end product. The 3D printing works exactly the opposite.

[2–6,8–10] The end product (say Taj Mahal model) is constructed by deposition of the material (e.g., Plastic) layer by layer on a platform by the printhead. The final product (a plastic Taj Mahal) is composed without wasting any material, and hence, this is called additive printing (adding layer by layer). The initial blueprint is in the form of a computer file (commonly produced by a computer app- computer-aided design [CAD]) which is fed into the computer attached to the 3D printer.^[4–6] Thereafter, the printing goes on without any additional inputs required and may take several hours to print depending on the size of the end product.

RP and DDM

The 3D printing has revolutionized the manufacturing industry. Conventionally, if one had to produce an industrial product (e.g. a metallic chair) first, it was designed by an artist/designer. Then, it was cast from a block of metal sheet, etc., assembled through molding, forging, welding, polishing, and finishing. It took a lot of time and material. If the product did not fulfill the desired requirements, then the whole process was repeated. With 3D printing, the whole process is very much simplified. It is called “RP.”^[14] The product is designed on computer with the help of CAD (or a 3D scanner is used to capture an image of a product in 3D).^[17] The model is printed by 3D printer in a smaller version. If it requires modification, it is quickly done on computer and is reprinted. If all is satisfactory, then a full-scale product is printed. When the desired features are approved, then it is straightaway taken for mass production by traditional method, e.g., injection molding. There are many components and parts of a machinery that can be directly 3D printed. This process is called direct digital printing.^[18] Taking our earlier example of Plastic 3D model of Taj Mahal, if we need any number of copies to say <100, we can directly print it on 3D printer using thermoplastic or any other desired material which 3D printers can use. This is extremely useful when one needs only a limited number of the final product, and hence, 3D printing is very economical and quick solution as compared to traditional way of mass production, e.g., injection molding.

Development Process

The process of 3D printing of an end product goes through several steps. These steps depend on several factors such as the material to be used, complexity of the product, environment where the product will be used, and cost and size of the end product.^[1–10] One simplified process is given below [Figure 1]:

Designing

A computer model is generated with CAD and computer-aided simulation studies can be done if required.

Software workflow

The CAD model is converted to buildable file and sent to the printer. This buildable file contains instructions for the printer how to build it layer by layer, sometimes incorporating

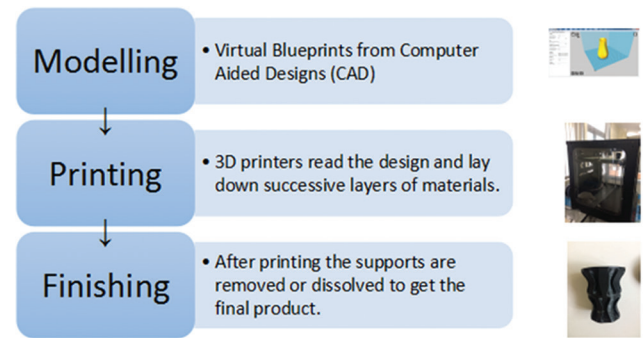


Figure 1: Three-dimensional printing involves three major steps. (a) Modeling (b) printing (c) finishing

instructions for any scaffolding material if required.

Material controls

The most important aspect of printed product is the material used. Choosing the appropriate material conforming to the desired strength, durability, usage properties, finish, and cost is vital.

Printing

The instructions are now ready to be delivered to the printer in the form of printable software file (most commonly G Code or AMF).

Post-processing

After printing, post-processing steps may be performed on the end product. These are removing residual debris, cooling (also called annealing), drilling, cutting, polishing, and if required, sterilization.

Process validation and testing

Sometimes, the end product is tested to make sure that the product has all the desired properties including functionality and strength. This may require individual components to be tested.

The American Society for Testing and Materials (ASTM) developed a set of standards to classify the additive manufacturing processes into seven categories “ASTM F42 – Additive Manufacturing.”^[19–22] These are:

Vat photopolymerization

In this method, a photopolymer resin is hardened with a UV light source.

- a. SLA: In this technology a liquid photopolymer resin is used and exposed to ultraviolet laser to build the product one layer by one at a time. After one layer is deposited and cured, then the second layer is deposited by the printer

head by descending equal to the thickness of a single layer, typically 0.05–0.15 mm. This process is repeated until the end product is ready.

- b. Continuous liquid interface production.

Material jetting

In this method, material is applied through a small diameter nozzle, layer-by-layer to build a 3D object, and it is then hardened by UV light.

Binder jetting

In this process, two materials are used, powder base material and a liquid binder. The liquid binder glues the layers together.

Material extrusion

This is a most popular method of 3D printing. One of the processes is called FDM. The term FDM is trademarked by Stratasys Inc. In FDM, a plastic filament or sometimes a metal wire is melted through a heated printhead nozzle and deposited layer by layer according to the CAD/computer-aided manufacturing instructions. To describe similar process, a trademark free term fused filament fabrication (FFF) was coined.

Powder bed fusion

This is also a very popular process of 3D printing. The most common method in this is called SLS. In SLS, a very powerful laser is used on plastic, metal, glass, or ceramic powders, layer by layer. Only that portion of powder is hardened where laser falls, and the rest of the powder layer acts as a scaffolding and is removed at the end to be reused.

Sheet lamination

In this technology, metal or paper sheets are used. The paper sheets are glued together and cut in the final shape. The metal sheets are joined together by ultrasound welding. This process is called laminated object manufacturing.

Directed energy deposition

In this technology, a metal wire or powder is deposited with the help of a robotic arm carrying nozzle and the material is hardened using high energy laser, electronic beam melting, or plasma arc.

Materials

The beauty of the 3D printing is that a large variety of material having different properties has been constantly added at a rapid pace.^[2,6,9,10] This has made 3D printing a universal tool. It can print objects as transparent, opaque, rubber-like, plastic, metallic, wooden, glass, and with any color of ones’

choice [Figure 2].^[2,7-10] The latest advances are in the field of biology where human and animal tissues are also used as a material for 3D printing.^[7] The choice of material depends on the final properties desirable in the end product. If you need biodegradable material, then polylactic acid (PLA) is a good choice, and if you need strength, flexibility, and durability, then nylon and acrylonitrile butadiene styrene (ABS) are good.^[23] The material used can be classified as:

Thermoplastics

These are used in powder form in sintering and filament form in FFF/FDM processes. It is the most commonly used material and is also used in various combinations. These are being already used extensively or are explored for future use: ABS, nylon a polyamide used for heat resistant properties, PLA which is biodegradable and used as a resin in SLA, and acrylic also called PMMA, polybenzimidazole, polycarbonate, polyethersulfone, polyetheretherketone (PEEK), polyetherimide, polyethylene (PE), especially ultrahigh molecular weight PE, polyphenylene oxide, polyphenylene sulfide, polypropylene, polystyrene, and polyvinyl chloride.

Ceramics

These are being increasingly used but need to be followed by firing and glazing steps. Gypsum is also used.

Paper

Standard A4 copier paper is used by the proprietary SDL process. The advantage is easy availability of A4 paper.

Wood

It is most commonly used in filament form in wood/polymer combination known as WPC.

Glass

MIT-mediated matter group and Micron3DP have used glass for 3D printing, mainly soda lime and borosilicate.

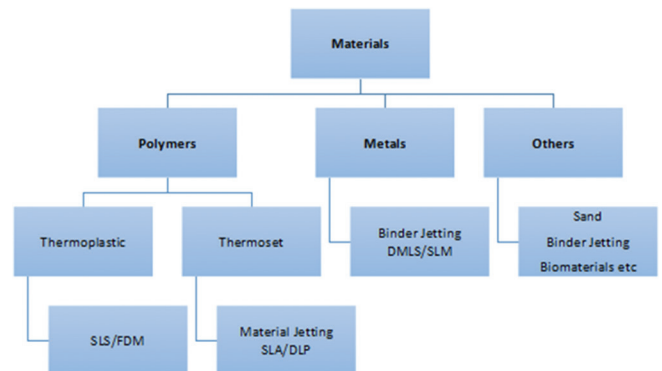


Figure 2: Materials in three-dimensional printing

Metal

Two most commonly used metals are aluminum and cobalt, but stainless steel, brass, silver, and gold are also used. Titanium is also being used in powder form.

Food

Chocolate is being extensively used for making food items by 3D printing. Others are sugar, pasta, and meat.

Combinations

Carbon fibers, thermoplastic polyurethane, and elastomeric polyurethane in combinations have been used. Stratasys has a proprietary (Objet Connex) combination of over 140 types of material by mixing the popular materials in various combinations.

Biomaterial

There are unique challenges to overcome when the artificial material is to be implanted inside the human body. The 3D structure should be compatible with other tissues and not evoke an immunological response. It must be able to function for a long time submerged in body fluids. The size and thickness vary from microns to millimeters to several centimeters.^[24–32]

Although the industrial 3D printers can now build layers of microns thickness, such as 16–75 μm resolution for SLA, 80 μm layer thickness for SLS, and 178 μm layer thickness for FDM, the human tissues require a vast range of sizes. The glomeruli of kidneys are ~approximately 200 μm in diameter, the human liver lobule is about 1.5 mm in diameter, and blood vessel networks ranging from micrometer (capillary) to multicentimeter (human aorta) may require multiple nozzles from 100 to 1000 μm size. The human tissues are categorized as macro-, micro-, and nanoarchitectures. The macroarchitecture is the overall shape of the organ or tissue, such as liver or bones; the microarchitecture is the layout of the tissue such as intercellular layout, porosity, and shape; the nanoarchitecture is surface modification such as differentiation, proliferation, or cell adhesion at molecular level.^[24]

The integration of RP, CAD, magnetic resonance imaging (MRI), and computed tomography (CT) has enabled printing of macro- and microarchitecture. Solid freeform fabrication is the type of RP that has facilitated designing and fabrication of complex biomedical devices. The biomaterials commonly used are living viable cells on scaffoldings of polymers (synthetic and natural), ceramics, and metals. These “Bioinks” contain living cells and is chemically or physically cross-linked with polymers to form hydrogels.^[24–27]

There are very few biodegradable and biocompatible biomaterials when using SLA technology. Multiple resins have been used for a single build with PEG-DMA and PEG-DA

with fluorescently labeled dextran and fluorescently labeled bioactive PEG within different regions of the scaffold. Newer macromers used are segments of PCL (three-armed hydroxyl-terminated), photo-curable poly (D, L-lactide), and PPF-DEF.^[24]

FDM technology in bioprinting has commonly used biocompatible polymers such as PCL and bioactive glass composites, PLGA with collagen infiltration, PCL coated with gelatin, PMMA, and PLA.^[24,28–31]

The SLS techniques can print scaffolds that required external architectures with porous interior structure. SLS process has used medical grade PEEK to make craniofacial implants. SLM was used to create a titanium mandible that accepts dental implants for a mandibular denture. Other materials used are PCL and HA with myoblast cells, SaOS-2 cells, human bone marrow stromal cells, and human osteoprogenitor cells.^[24,25,27,31,32]

3D bioplotting and biofabrication are relatively newer techniques being used increasingly. Bioplotting materials include PLGA, TCP, collagen and chitosan, collagen-alginate-silica composites coated with HA, soy protein, and agarose with gelatin.^[33–36] These are used with human umbilical vein smooth muscle cells, human skin fibroblasts, rat primary bladder smooth muscle cells in collagen droplets, human microvascular endothelial cells in fibrin, and alginate droplets^[33–36] Furthermore, there is bioprinting of single cells and cell-laden hydrogel-PCL scaffolds^[37–41] Block cell printing, a high throughput printing of single-cell arrays, has been achieved.^[37] Biggest advancement will be to incorporate precision injection molding into 3D Printing.^[37–40]

An open source library for medical 3D printing researchers can be accessed at www.thingiverse.com or the National Institutes of Health's 3D-Print exchange (3Dprint.nih.gov).

Choosing the Right Printer

The two big commercial names for 3D printing are 3D systems and Stratasys. Many new low-cost generic 3D printers are now available in the market starting from around Rs 50,000. The biggest question for beginners is how to choose the right printer. It depends on what will be the end product. Will it be used inside the human body or outside? What temperatures it needs to withstand? Are many colors needed or will it be transparent? How strong, durable, and flexible it should be? Does it require electric conductive material inside it or living tissues? How complex is the final geometry, like solid from outside and porous from inside and how big is the size of end product? What is the resolution needed in dots per inch, Z-layer thickness, pixel size, beam spot size, and bead diameter? Other practical features are the cost, speed of printing, ease of printing, footprint size, noise level while printing, and available software for designing, after sales service such as availability of parts, raw material, and service engineers.^[17,42–45]

Hence, depending on the functionality and physical properties needed in the end product, one has to choose the technology of 3D printer required, for example, SLA, FFF/FDM, and SLS/SLM. The other important things are the type of raw material needed for 3D printing, filaments, powder, resin, metal, software, or biomaterial and definitely the cost of the printer. [42,43,45]

For manufacturing industry, the FDM/SLA and SLS technology printers are most commonly used. They work with thermoplastics and carbon fibers in various combinations. For printing biomaterial, extrusion or inkjet printer is the ideal choice. [25,37,45]

Uses

1. The most common commercial usage is RP.[32] Almost all types of industries now use 3D printers for RP.[32] Only once convinced of the product, they go for mass production by traditional methods. Household products, heavy engineering machines, automobile industry, aerospace and aviation industry, food industry, electronic products, architectural scale models, reconstructing fossils or ancient artifacts, gift items and creative 3D modeling as art form, toys, instruments, and equipments, fashion designing like bikini, shoes, clothes, jewelry or museum souvenirs etc are produced using the technology of 3D printing and RP [Figure 3].[2,4-6]
2. In medical field, it is used for making customized prosthetics, orthotics, or implants. It is also used for printing laboratory equipments and as research tool for biomaterial printing with the ultimate goal of printing organs for transplantation. It is widely used for simulated surgeries on patients’ anatomical 3D-printed structures.

Following are some of the biomaterials being printed for clinical use by 3D printers. [7-11,46-49]

3. In patients of tracheobronchomalacia, airway splint implant had been successfully tested in three children as of April 2015. The splints are quickly printed and cost about \$10 per unit.
4. A bionic ear has been printed incorporating electronics to hear sound frequencies which even normal humans cannot hear.
5. Scientist has successfully 3D-printed skin for burn victims which could be grafted in the patients to accelerate healing.
6. A major advancement is the use in printing customized prosthesis and orthosis. Patients who lose various bones to cancers or infections are getting customized bone-like material as grafts by 3D printing and 3D scanning. 3D printed casts have also shown to enhance healing 40–80% faster than traditional casts.
7. In war-torn Sudan, many persons have lost limbs in blasts or land-mines. “Not Impossible Labs” from Los Angeles, California trained locals to print and custom fit these very inexpensive prosthetics.
8. Many customized dental crowns, bridges, implants, and other dental restorative and prosthetic devices are now 3D printed.



Figure 3: Representative images of applications of three-dimensional (3D) printing. (a) Customized chair in car, dental implants, umbilical cord cutter, skull part after craniotomy, foot spine, and pelvic bone models. (b) Geometric complexity is never a limitation of 3D printing

9. 3D-printing is helping to quickly print and test new shapes of pills/tablets to see if it can improve drug release rates. Lee Cronin, at the University of Glasgow, describes a 3D printer capable of printing drugs at the molecular level. Louisiana Technical University researchers have printed medicines delivery system for bone cancer patients.
10. Researchers at York University, Canada, has 3D printed three types of cardiac tissue - contractile cardiac muscle cells, connective tissue cells, and vascular cells to beat in sync with each other. "This breakthrough will allow better and earlier drug testing, and potentially eliminate harmful or toxic medications sooner," said Professor Muhammad Yousaf from York University.
11. Harvard University researchers have published papers on bioprinting blood vessels integrated tissues. This has opened a whole new way to do *in vitro* research and avoid expensive tissue culture and animal model studies for drug development or a novel treatment modality.
12. Using MRI and CT scan data from individual patient, 3D model is constructed which is variously used for printing perfect fitting prostheses, orthoses, and implants or making virtual reality applications to practice the complex high-risk surgeries on 3D models before doing the surgery in the real patient. With the advances in tissue and blood vessel printing, it is very close to the real-life situations as one wrong step actually results in blood splashing out of the artery. This has made possible repeated practice sessions until one masters the surgery. It is very important in complicated neurosurgery cases or when faced with a rare surgery which one has never performed earlier.^[2-6]
13. Professor Sushmita Bose of Washington State University created intricate bone scaffolds of chemicals and ceramic. This may eventually be used for growing bone in patients who have lost bony tissues due to injury or cancer.
14. Jonathan Butcher, at Cornell University, used a combination of alginate, smooth muscle cells, and valve interstitial cells, to print a heart valve which was tested in a pig.
15. 3D-printed intervertebral discs, wedge for wedge osteotomy, scapula implant, femoral head and neck jigs, pre-contoured plate for acetabulum fracture, and customized iliac prosthesis, and some surgical tools such as forceps, hemostats, scalpel handles, and clamps have already been used in hospitals.
16. James Yoo at the Wake Forest School of Medicine in the US has developed a system to scan the wound and directly print skin tissue layers in the wound itself so that healing is faster and chances of infection are less.

Organovo has commercially launched 3D-printed liver cells that are able to function for >40 days. This will help in *in vitro* testing of drugs and study the mechanism of cancer spread in the body.

Role of 3D Printing in Medical Field^[7-11,46-49]

Since the time of its inception in 1983, the use of 3D printers has been diversified. The first 3D printer was just a cup and ordinary looking. However, it paved way for a health-care revolution. Here are some of the ways in which 3D printer is being already used in healthcare industry.

Prosthesis development

In a recent case, a person came complaining that her robotic suit was not comfortable. Despite the efforts by the assistive technology team, the patient did not show satisfaction with the suit. She was paralyzed below her waste and though the suit gave her the independence to move but limited the symmetry and freedom of movement.

Unlike such prosthesis, the 3D-printed prosthesis is custom tailored for each individual. By digitally capturing her measurements, a custom fit suit was made which gave her independence to move around.

The similar technology is now being used to create customized scoliosis brace, supports for amputees, and devices to measure clubfoot deformity.

Tissue engineering

Medical technology is building tiny organs using the principals of 3D printing with stem cells as the production material. These small organs, once build, will be in future be able to grow inside the body of a sick patient and take over when an organic organ fails.

Skin for Burn Victims

It is well known that the skin grafts are difficult to obtain and provide terrible esthetics. Since a long time, the burn patients have little options to treat their burnt skin. 3D printing technology may be able to provide a solution for the same. It has been shown by researchers in Spain that same careful layer-upon-layer approach can make a 3D bioprint prototype that can produce human skin.

Drug Development

A 3D-printed pill may house multiple drugs at once, each with different release time. This is called a polypill concept and has already been tested for patients with diabetes. This holds a lot of potential in future.

Social change

The revolution in online shopping is already happening, but the products are still sent through rail/air and land. However, with

3D printing, all this may change and people will be printing products in their homes or backyards. Hence, the volume on freight services may also ease.

3D Model libraries

There are websites called 3D marketplace such as Thingiverse, Myminifactory, CG Trader, and Pinshape which contain several million 3D model files one can download for free or a small charge.^[50-55] Another search engine called Yeggi has .STL files of several everyday use items. RepRap is a wiki-based website that is trying to bring 3D printing to everyone.

A word of caution

Every new technology comes with its share of problems. The ease of 3D printing has resulted in the issues such as ethics, morality, and the disposal of waste generated. The National and International Laws need to be formulated and implemented so that people do not manufacture weapons or counterfeit currency and issues of violation of patent rights etc.

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