# Medical Applications for 3D Printing: Recent Developments

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**With the development of printing techniques and materials suitable for particular medical applications, research interest is increasing.**

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## Abstract

**This is a review of some of the recent developments in the application of 3D printing to medicine. The topic is introduced with a brief explanation as to how and why 3D is changing practice, teaching, and research in medicine. Then, taking recent examples of progress in the field, we illustrate the current state of the art. This article concludes by evaluating the current limitations of 3D printing for medical applications and suggesting where further progress is likely to be made.**

## Introduction

The American Society for Testing and Materials (ASTM) International Committee F42 has adopted the term additive manufacturing (AM) for techniques which produce physical objects from three-dimensional (3D) digital data via the “process of joining materials to make objects from 3D model data, usually layer upon layer, as opposed to subtractive manufacturing methodologies”.[1] This refers to a series of industrial AM processes commonly referred to as 3D printing, which employ computer-automated manufacturing (CAM) processes to fabricate physical 3D objects layer by layer from computer-aided design (CAD) models. Thus additive manufacturing, commonly known as 3D printing, is a manufacturing method in which objects can be created by fusing or depositing materials onto, or into, a substrate. The materials deposited can be powders, plastics, ceramics, metals, liquids or living cells, making the process hugely versatile. The process is also repeatable, accurate, and cost-effective for small production runs, allowing the reliable production of customized parts. It also allows fast production and collaboration between physicians and researchers, who can now share a physical object over the internet and recreate it quickly with high precision.[2]

The technology, history and operation of 3D printers has been described elsewhere.[3,4] This paper focusses on the medical applications of 3D printing, presents recent research, and its implications for medical applications. We have defined categories of medical applications to classify existing research into 3D printing in medicine. Each is described in brief below:

## Surgical Planning

One of the possible applications of 3D printing that have emerged is surgical planning. This involves studying the anatomy and physiology of defects in complex organs such as the brain or the heart, or anatomical specimens such as the pelvis or the spinal cord, and using the information for surgical planning. 3D models can assist surgeons to study the impaired organs before the operation, explore various approaches and acquire hands-on experience before entering the operating room. This process shortens operation time significantly, and ultimately improves the outcome of the operation for the patients, the surgeons, and the patients' care providers.

## Prostheses

Recent advancement in 3D printed patient-specific prostheses allows a wide range of disabled people affected either by an accident or a genetic deformity to carry on their normal life.[5] With the aid of high quality imaging technology, 3D printing has the capability to create a precise anatomic prosthesis used in various medical applications.[6,7] This has also made significant impact on the field of dentistry.[8,9]

## Medical Education and Training

Using cadaveric materials to train novice medical physicians has been the subject of controversy. This is both due to ethical issues as well as the cost of the processes. 3D printing techniques may offer a novel and effective substitute by reproducing accurate complex anatomical organs from high resolution CT imaging for many cases, including those in which using a cadaver is not an option. In addition, the ability of 3D printing to reproduce a number of copies of any anatomical subject in different sizes gives a great advantage in training facilities.[10]

## Medical Research

The advent of printers gentle enough to print cells directly has resulted in the automated production of cell structures for toxicity testing, and the development of new treatments for various diseases and tumors. Up to 50% of drugs that pass preclinical testing are later found to be toxic to humans, while others may be non-toxic to humans despite being toxic in animal testing.[11] Consequently, the ability to reproducibly print tissues which match the actual cellular arrangement in natural tissues and organs allows researchers to accelerate the research process. Here we describe some of the recent advances in medical research for these applications.

## Organ Printing

3D printing is already used in the production of human organ and tissue structures for research, as described in the medical research section. These can be integrated with biocompatible microfluidics to create highly complex structures to mimic the function of native human organs.[12] The next step is printing organs that can be transplanted into human donors, or even printing organs in the body in-situ in the operating room. While this technology is less mature than others described in this article, it has the potential to revolutionize medicine, making organ transplants and current synthetic artificial organs obsolete.[13]

## Drug Delivery

Drug delivery will undoubtedly change as 3D printing becomes integral to pharmaceuticals. Drugs can be printed not only in specified doses for each individual, but with multiple sustained release and immediate release layers, which allow the dosage profile to be modified. This enables personalized treatments, and also helps patients under heavy medication, who may be able to reduce the number of pills they need to take. 3D printed drug delivery devices which fit exactly to the anatomy of a patient are also under development.

The breadth of fields described in this introduction shows how much 3D printing technologies are changing medicine. In fact, the applications of 3D printing in medicine are now so numerous that an exhaustive and comprehensive study of them all is practically impossible. Several recent reviews have examined one particular field, such as Mehndiratta et al.'s review of 3D printing based on medical imaging,[14] Martelli et al.'s review of 3D printing in surgery[15] and Pati et al.'s review of bioprinting for tissues and organs.[16] This review will look at developments from within the last three years (from 2014 to date) in each of the applications we have defined above to demonstrate the current state of the art.

## Latest Developments by Application

### *Surgical Planning*

Operational surgery on a complex congenital heart requires a highly skilled and experienced surgeon who can also make quick decisions during the operation. Making instantaneous decisions during the operation inevitably may lead to longer operating times, which may cause adverse impacts on the surgical outcome. Vodiskat et al. used 3D printing model of the congenital heart defect used for preoperative planning.[17] They have employed two different commercially available 3D printing technologies (Polyjet Objet Eden 350, MakerBot Replicator) for reconstruction of the congenital heart defect in three different patients.

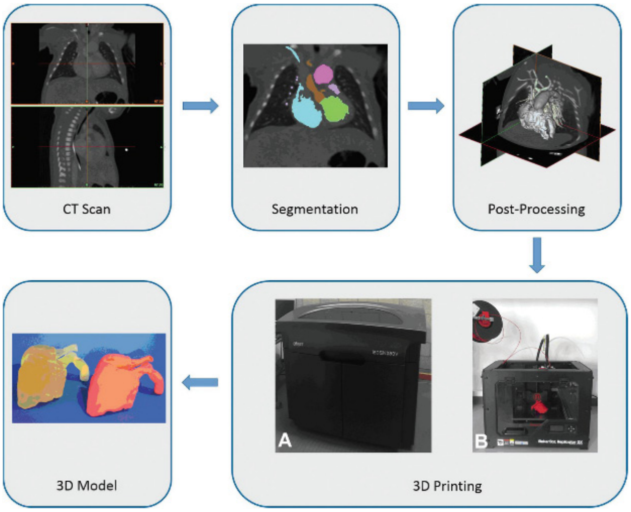

**Figure 1**. Flowchart of creating a 3D printed model of congenital heart defects from CT scan data.[16]

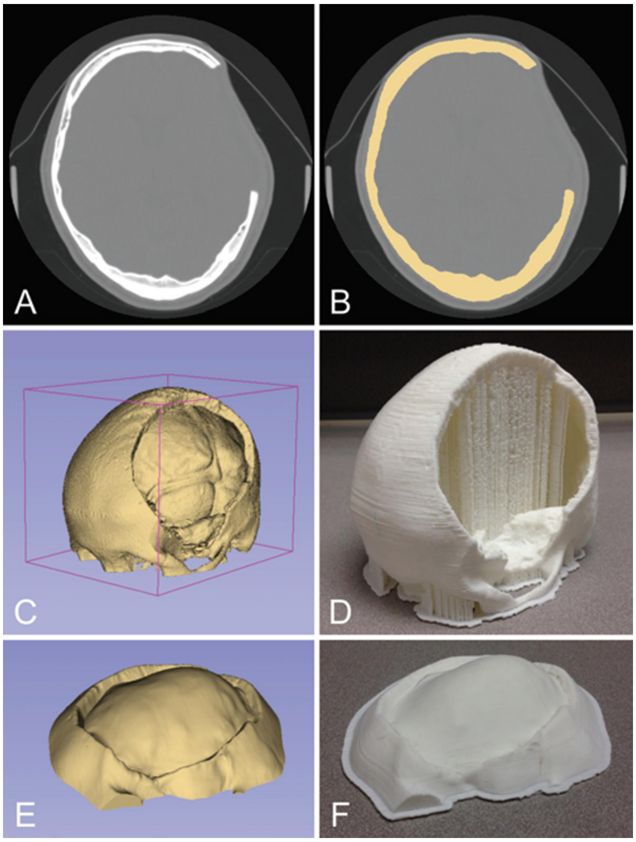

**Figure 2**. 3D printed skull and mold (D,F) from high resolution CT scan data (C,E) using the fused deposition modelling method.[20]

Their methodology is shown in Figure 1. They concluded that, provided that an excellent CT scan data is available, a cost-effective 3D printed model can be created to be used for preoperative planning.

Old pelvis fracture is one of the most challenging fractures to fix. This is mainly due to the complex anatomy of pelvis and the difficult access to the operational sites. Wu et al. evaluated the use of 3D printed pelvic models for preoperative planning.[18] Over the course of four years, they studied nine different clinical cases, and evaluated their surgical reconstruction based on the 3D printed models of the fractured pelvises. They demonstrated that there was a good correlation between the preoperative planning and postoperative results extracted from X-ray examination in all cases. They recommended higher numbers of patients are required to further consider the use of 3D preoperative models for the pelvis fracture surgery.

Truscott et al. presented three case studies of 3D printing models that can assist surgeons with preoperative planning. They created 3D model of pelvis and femur, eye socket and scapula from the corresponding CT scan data.[19] They used 3D printing laser-sintering technology to make an eye socket out of Titanium. They concluded that, in comparison to a CNC process, using this technique minimizes the amount of material wasted.

### *Prostheses*

In a study conducted by Suaste-Gómez et al. an ear prosthesis was 3D printed using polyvinylidene fluoride (PVDF).[20] The prosthesis response to pressure and temperature was studied using an integrated astable multivibrator circuit. Their novel 3D-printed PVDF-made ear prosthesis showed high sensitivity to pressure changes. This is a promising result for extensions of this technique to other fields of biomedical engineering.

Commercial patient-specific cranioplasty prostheses are very expensive. Alternatively, acrylic bone cement is widely used in the field as a cost-efficient approach. However, the manual fabricating of the bone cement is cumbersome and may not lead to a satisfactory implant in many cases. Tan et al. created a 3D printed skull from high resolution CT scan data using FDM.[21] The mold was used as a template to shape the acrylic implant. They showed that their approach to make patient-specific acrylic cranioplasty implants with a low-cost 3D printer is successful; however further studies are required to assess the application in the clinical setting. The printed prosthesis and CT scan data are shown in Figure 2.

Ahlhelm et al. combined the 3D printing lithography-based ceramic manufacturing technique with so-called

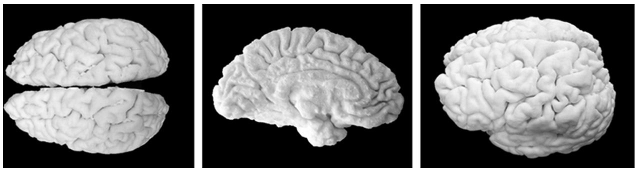

**Figure 3.** Anatomically accurate 3-D printed brain model.[24]

freeze-foaming technique in order to achieve inherent open-porous-interconnected foam structures of the bone.[22] They demonstrated that these novel potential bone replacement structures might serve as possible next-generation material which can be used for personalized implantation.

In a study conducted by Parthasarathy et al. a novel design approach for creating periodic cellular structures was proposed.[23] The material was fabricated using a metal 3D printed technique. They concluded that 3D printed implants, made out of the proposed material, would fulfil the need for lighter implants and meet the esthetic and functional requirements for patients with skull defects.

3D printing techniques have been used recently to reproduce patient-specific tissue-mimicking materials. In a study by Wang et al., two types of dual-material 3D printed meta-materials were designed to replicate the properties of soft tissues.[24] They showed that the proposed 3D printed materials have great potential in fabricating patient-specific tissues. Advantages included accurate mechanical properties, which can vary depending on gender, age, ethnicity, and other physiological/pathological characteristics.

### *Medical Education and Training*

In general, 3D-printed models are anatomically accurate, provided that high quality CT scan data are available. However, in many cases 3D-printed models are typically inflexible, which makes application difficult in cases involving soft tissue, such as the brain. Ploch et al. proposed a very fast and cost effective method using combined 3D printing, molding, and casting, to create realistic models of human brains which are physiologically accurate as well as deformable.[25] They used a surrogate gelatin-type material that closely mimics the mechanical properties of the human brain. Their models are shown in Figure 3. They concluded that this technique can be used to make personalized deformable brain models, which can be used for surgical planning or for medical training.

A study by McMenamin et al. presented crucial elements which directly or indirectly affect the accuracy of the 3D printed replica of human anatomical objects for training purposes.[26] They discussed the required image data quality, which can potentially produce high quality replicas. They also presented a cost analysis of making a 3D printed replica in comparison with other alternatives. They concluded that the 3D printing is the most rapid and economic technique to reproduce human specimens for medical education. They demonstrated that realistic 3D printed replicas require many scans.

### *Medical Research*

The development of 3D printing for modelling the behavior of cancers has a huge impact on assessing the viability of the responses of the various forms of the disease to different treatments. Using HeLa cells, researchers at TsingHua and Drexel Universities have defined a process to deposit HeLa cells into a 10 x 10 x 2 mm hydrogel structure to create synthetic cervical tumors to investigate the growth of the disease.[27] Alongside this they created similar tumors using existing 2D methods. They report that their model showed different behavior from previous 2D models, proliferating more quickly and forming cellular spheroids. They note that this method can be especially effective if combined with techniques to deposit multiple types of cell, and investigate the microcellular tumor environment.

The development of microfluidics in bioprinting allows: better control over experiments on 3D cell cultures; and the move towards more complex tissue structures like those in native tissues. Researchers at Drexel University have created cell-laden 3D microfluidic structures embedded in PDMS with improved leak protection compared with existing structures.[28] This innovation allows them to guide cells through the microfluidic network to create complex tissue structure. They report a material deposition repeatability of 10 $\mu$m with their custom-made deposition apparatus, and the capacity for heterogeneous cell co-cultures using a dual nozzle process. This is part of a large body of work improving the integration of microfluidics with cell cultivation to facilitate all kinds of medical research.

3D printed cells in hydrogel scaffolds have been used by researchers in the University of Dresden to grow cultures of microalgae and microalgae/human cell combinations.[29] The microalgae, exposed to light, were able to grow quickly and the chlorophyll content increased 16-fold over the first few days. The

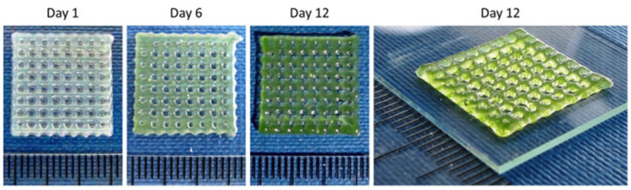

**Figure 4.** Growth of algae within the impregnated hydrogel at 1, 6 and 12 days.[28]

progress of the algae over 12 days is shown in Figure 4. The microalgae were capable of delivering oxygen to the human cells closely patterned in their midst. The researchers claimed that the principle of such a technology delivering oxygen or secondary metabolites as therapeutic agents was proven, but noted that much effort was still required to bring about any feasible therapies with their technology.

### *Organ Printing*

Researchers at Cornell University demonstrated the 3D bioprinting of full-size tri-leaflet heart valves using hydrogels as a scaffold for the cells.[30] They print two different cell types: aortic smooth muscle cells; and aortic valve leaflet interstitial cells onto the prefabricated hydrogels. The cell-impregnated sections retained their tensile strength and were viable over seven days in culture. The printed cells had good spreading, resulting in a robust structure, and high phenotype retention, indicating they functioned as intended. They note, however, that the tensile strength of the resulting prototypes was too low to function properly as a heart valve, and made several recommendations for future work. These include the inclusion of microfluidics to promote more robust cell growth. The CAD design, fabrication process and resulting valve are shown in Figure 5.

Researchers in Edinburgh describe the fabrication of functioning "mini-livers" using 3D printing.[31] Their innovation is the printing of fragile hiPS cells in to a 3D alginate hydrogel matrix without damaging their viability or pluripotency. The cell structure was viable for 24 days after the printing. The pluripotency was measured by secretions of albumin, which peaked 21 days after the printing. The work is aimed at animal-free drug trials and personalized medicine, but shows that capability of the 3D printing technique using cultivated, patient-specific cells to produce 3D structures that are viable for weeks after printing and function as a native liver.

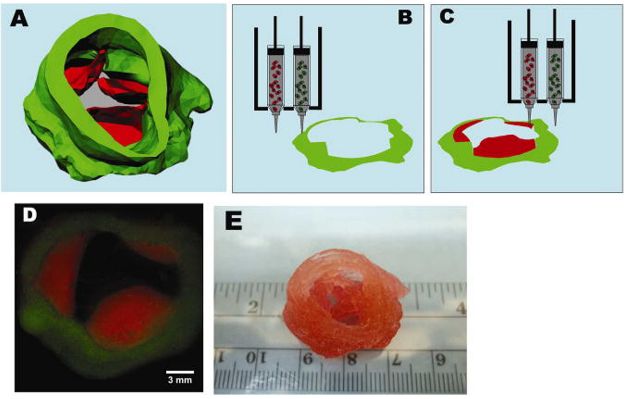

**Figure 5.** The bioprinting of an aortic valve conduit. (A) Computer model, (B) Printing a layer of SMC, (C) Printing a layer of VIC, (D) Flourescent image of first two layers, (E) The resulting aortic valve conduit as printed.[29]

Finally, the capacity to create organs matching the complexity of native organs brings about the distant possibility of improving these organs, or fabricating entirely new organs for specific functions. An international group of researchers in evolutionary biology have looked beyond the current state of the art and created a 3D morpho-space to describe not only biological structures in human organs but also cells and animal structures, including invertebrates.[32] The design space has on the three axes cognitive complexity, solid/liquid and developmental complexity. They note that a large section of the design space is a void, and bioprinting techniques allow this space to be explored to explore entirely new biological configurations and investigate fundamental questions about evolution.

### *Drug Delivery*

Researchers at University College London have fabricated topical drug delivery systems using 3D bioprinting.[33] They investigated fused deposition modelling (FDM) and stereolithography (SLA) for the fabrication of devices to be worn on the nose and deliver salicylic acid for the treatment of acne. The salicylic acid is loaded into commercial polymer filaments using hot melt extrusion. 3D printing lends itself to this process, as scanned images of the patient's anatomy can be used to create devices that fit exactly, maximizing contact and delivering an even dose of the drug. They found that while both methods created suitable devices, the SLA method was more convenient as a fabrication process. The dosage can also be varied when the filaments used for printing are prepared.

To demonstrate the capacity of 3D printing to produce drug tablets of sufficient quality for prescriptions,

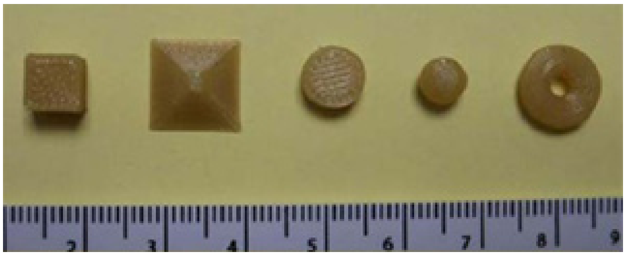

**Figure 6.** Cube, pyramid, cylinder, sphere and torus paracetamol tablets fabricated by Goyanes et al.[34]

Khaled et al. at the University of Nottingham attempted to print Guaifenesin Bilayer tablets (Mucinex) using a desktop 3D printer bought for under $1,000.[34] They compared the drug release profiles for their designs, and found that one of them showed a cumulative drug release profile that remained within 10% of the release profile of the commercial drug over a 14 hour dosage cycle. They also evaluated the weight variation, hardness, thickness and friability of the tablets they had produced.

Given the new design freedom that 3D printing in pharmaceuticals provides, Goyanes et al. investigated the effect of different shapes of tablet on drug release profiles.[35] They investigated torus, pyramid, cube, sphere and cylinder shapes using an FDM process to print paracetamol-loaded filaments of PVA. Their printed tablets are shown in Figure 6. They first demonstrated that the stability of the drug was unaffected by the printing process. They then investigated the amount of the drug that was released in each tablet and showed, as expected, a clear dependence on surface area to volume ratio. They state that these complex geometries would be impossible to fabricate using traditional powder compaction methods, and will allow better control over drug release profiles.

## *Discussion*

This paper has described a large range of applications for 3D printing and bioprinting in medicine. Here we will look at lessons learned from some of these recent developments, and try to make some realistic predictions for the future.

For many surgical operations, comprehensive evaluation and surgical planning are essential to achieve good results. In addition to conventional imaging examination, the 3D printing models of the affected organs or anatomies greatly assist surgeons to explore various options before entering the operating room.[15] 3D printed models created from a high quality CT scans assist surgeons to understand the feasibility of the operation plan, shorten the operation time, and consequently improve the outcomes.

3D printing techniques have shown a significant capacity to produce patient-specifics prostheses that fully satisfy the esthetic and functional requirements of patients. The process of creating a 3D printed prosthetic is much quicker and less expensive in comparison to other alternative solutions. The 3D printing anatomical model can also be a great substitute to the conventional cadaveric material in training. They can improve surgical training with the ultimate goal to provide accurate, customized, high precision treatment.

3D bioprinting in research is continuing to mature, and its capacity to provide more accurate models in research of diseases such as cancer is demonstrated by the work of Zhao et al.[15] The integration of microfluidics with 3D bioprinting to build complex cocultures and tissue structures, as shown in the work of Snyder et al.,[16] is the subject of increasing research interest. This integration of the two disciplines may be the key to allowing the creation of working organs, as discussed in more detail below. 3D bioprinting has also facilitated research on early conceptual work for new therapies, exemplified by the work of Lode et al.[17]

The printing of full scale biological organs is still a long way from being a reality. The cases described here show that even at the current state of the art, fabricating a robust heart valve using cell printing is a long way from being a reality: while the resulting cell culture is robust in biological terms, current techniques do not allow the creation of a structure with the required structural integrity.[29] Printing a full organ currently remains an aspiration not because functional cells cannot be printed, but because the structure remains too complex for existing methods. Developments in the hydrogel matrices, printing techniques, and better integration with microfluidics are all important steps to move towards obtaining functioning, robust artificial organs by bioprinting. The latest bioprinters have the capacity for extrusion of angiogenic microfluidic networks alongside the tissue printing.[30]

The concept of 3D printers appearing in pharmacies is now close to being a reality. The possible benefits to this work are clear from the papers cited here. The 3D printing process for acne treatment shows how personalized drug delivery can truly become, with both the anatomy of the patient and their required dosage being considered in the fabrication of a personalized device[3.2] The fabrication of pharmacy-quality tablets using an inexpensive printer by Khaled et al.[33] indicates the increased prevalence that printers may have in pharmaceuticals in the near future. The ability to print complex geometries in tablets will allow drug release to be controlled with more precision.[34] This is clearly one of the areas of 3D printing in medicine where the technology is mature and the practicalities of its deployment are now worth consideration.

3D printing is a method for conveniently creating customized one-off objects, and is transformative in a great number of medical applications. With the development of printing techniques and materials suitable for particular medical applications, research interest is increasing. The recent developments described here show that, while exciting and important advances have already been made in areas of research, teaching, surgical planning, and prosthetics applications like personalized drugs and organ printing are at an early stage of development.

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## Disclosure

None reported.

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