## Chapter 3

# 3D Printing of Biopolymers: Trends and Opportunities for Medical Applications

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Overall, three-dimensional (3D) printing is a technology booming for processing and development of unique polymeric materials. In this context, the manufacture of parts layer-by-layer with specific requirements such as biomedical devices and tissue engineering may represent an economical option, offering the flexibility of starting materials. However, there are many outstanding challenges to meet. This chapter provides an overview of the field of 3D-printed biopolymers for medical applications, and future trends and opportunities in this field.

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## 3.1 Introduction

Since the past decade, tissue engineering has shown a sensational promise in providing more viable alternatives to surgical procedures for harvested tissues, implants, and prostheses. Due to the fast development on biomaterial technologies, it is now possible for doctors to use patients' cells to repair orthopedic defects such as focal articular cartilage lesions. In order to support the three-dimensional tissue formation, scaffolds made by biocompatible and bioresorbable polymers and composite materials, produced by three-dimensional (3D) printing, for providing temporary support to the damaged body and cell structures have been developed recently. Although ceramic and metallic materials have been widely accepted for the development of implants, their non-resorbability and necessity of second surgical operation result in extra discomfort for the patients and limit their wide applications [1].

3D printing is also known as additive manufacturing (AM), layered manufacturing, rapid prototyping (RP), or solid freeform fabrication. This technique represents the direct fabrication of parts layer-by-layer, based on data obtained by computerized medical imaging equipment such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, using a computer-aided design (CAD) file [2]. In 3D printing, CAD models of the parts to be manufactured are first sliced in a virtual environment to create a stack of two-dimensional (2D) slices. A 3D printing machine then builds the parts one layer at a time based on the 2D slice information, stacking and joining successive layers to make the final 3D object. Just as the Internet has given us the ability to access information and connect with people from different parts of the world, CAD has provided us the ability to create, modify, and, if needed, critique designs in a virtual world. With the advent of 3D printing, such virtual designs can now be rendered into physical 3D objects that can serve as prototypes or be directly used as functional parts for a variety of applications. In this context, polymers in various forms, reactive, liquid solutions or as thermoplastic melts play a key role in many

applications and the further expansion toward manufacturing robust, real end use products [3].

The origins of contemporary 3D printing can be traced back to the 1980s when Hull invented stereolithography (SLA), the first 3D printing technology [4]. SLA is a process in which an ultraviolet (UV) laser light source is focused onto the surface of a UV-curable liquid monomer bath and scanned in patterns representing slice cross sections. The scanned monomers undergo photo-induced cross-linking and harden to form the desired 2D cross sections, while the uncured monomers remain in the bath. Hull was also the first to find a way to allow a CAD file to communicate with the RP system in order to build computer-modeled parts. Hull's patent was approved in 1986, making it the first patent for a 3D printer. The company 3D Systems, founded by Hull, focused on commercializing SLA systems, which were the first commercial 3D printers [5].

Fast forward to 2014, when the U.S. National Aeronautics and Space Administration (NASA) launched the first 3D printing machine to the International Space Station to directly build parts in space under zero gravity [6]. This is also the year when researchers from Oak Ridge National Laboratory built a complete car body using a 3D printing technique known as big area additive manufacturing and partnered with Local Motors to commission and drive a functional car at the International Manufacturing Technology Show [7]. 3D printing-based agile manufacturing technologies are promoting on-demand production with traditional as well as innovative designs that are difficult, if not impossible, to make through conventional manufacturing (CM) approaches. 3D printing technologies are also making a significant impact in biomedical research—from device designs to tissue engineering (TE) to bioprinting and drug delivery.

After following the technology, markets, and publications over several years, it appears that now we are in a period where many decisive actors in industry, media, and research and even finance advisors realize that the traditional area of prototyping is expanding more and more into manufacturing, and this will have a significant impact on many areas of our lives, and probably a spectacular growth of the 3D printing industry [3].

## 3.2 Brief History of 3D Printing

Several 3D printing technologies were conceived and developed around the time of the emergence of SLA. Deckard invented selective laser sintering (SLS) as a graduate student in Beaman's group at the University of Texas at Austin [8]. SLS uses powder materials spread on a build plate where a laser selectively sinters the powder in certain areas based on the CAD file [6]. A similar powder bed-based concept formed the basis of another technology, 3D printing, at the Massachusetts Institute of Technology by Sachs' group. Inkjet printing was combined with a powder bed, where a binder was printed onto each successive layer of swept powder based on the CAD slice information. Using this approach, complex shaped metal, polymer, and ceramic parts could be printed. However, post-processing or sintering steps were often required to enhance the final strength of the parts [9]. Scott and Lisa Crump developed another 3D printing technology called fused deposition modeling (FDM). FDM involves heating a thermoplastic filament to a semi-liquid state, which is then extruded and deposited through a nozzle onto a substrate to build parts layer-by-layer based on the CAD file information [10, 11]. Additionally, Sanders released the first 3D printer based on inkjet printing of thermoplastic polymers [12]. Parts with fine features could be made easily using this approach. These are some of the notable early-stage 3D printing technologies that were primarily focused on RP for design verification and visualization.

Over the past 15 years, a variety of new technologies have evolved that have transformed the idea of RP to AM, where parts produced by a 3D printer can be directly used for a variety of applications. In the case of metallic materials, laser-based or electron beam-based technologies with or without a powder bed have truly revolutionized industrial applications of these printers. For biomedical applications, novel fabrication approaches based on the 3D-Bioplotter or direct ink writing, laser-assisted bioprinting, and robotic-assisted printing are all in use for different applications. Table 3.1 offers a brief summary of some of these technologies that are relevant for biomaterials and their applications toward TE [13–26]. Other technologies related to metallic printing are covered throughout this chapter.

**Table 3.1** 3D printing technologies and their applications in biomaterials

| Technique | Process details | Processed materials for tissue engineering | Advantages and disadvantages | References |
|---|---|---|---|---|
| 3D plotting/direct ink writing | Extrusion-based layer-by-layer deposition | A variety of polymers and ceramics have already been used, including polycaprolactone (PCL), hydroxyapatite (HA), bioactive glasses, polylactic acid (PLA)/polyethylene glycol (PEG), and poly(hydroxymethyl glycolideco-$\varepsilon$-caprolactone) | **Advantage**<br>–Easy to incorporate both drug and biomolecules (proteins and living cells)<br>**Disadvantages**<br>–Post-processing may be needed for some materials<br>–Process works well within a certain range of viscosity | [13–16] |
| Laser-assisted bioprinting | Coating the desired material on transparent quartz disk (ribbon); the deposition is controlled by laser pulse energy, and resolution is controlled by distance between ribbon/substrate, spot size, and stage movement | A variety of materials, including HA, zirconia, HA/MG63 (osteoblast-like cell), human osteoprogenitor cell (i.e., a cell that has the potential to transform into one that forms bone), and human umbilical vein endothelial cell | **Advantage**<br>–Ambient and mild condition is suitable for organic and inorganic materials and cells<br>**Disadvantage**<br>–Homogeneous ribbons are needed | [17, 18] |

(*Continued*)

**Table 3.1** (*Continued*)

| Technique | Process details | Processed materials for tissue engineering | Advantages and disadvantages | References |
|---|---|---|---|---|
| Selective laser sintering | A powder bed-based process that partially or completely sinters layer-by-layer using a laser-based heat source | A large variety of polymers, metals, and ceramic materials have been used with this technique, including PCL, HA, PLLA, tricalcium phosphate, and poly(3-hydroxybutyrate) | **Advantages**<br>–Powder bed is used as support, therefore no need for secondary support structures<br>–Can be used for a variety of materials<br>**Disadvantage**<br>–Feature resolution depends on laser-beam diameter | [19, 20] |
| Stereolithography | Layer-by-layer fabrication by exposure to photopolymer liquid; polymer solidifying at the focal point, and un-exposed polymer remains liquid | A large variety of photo-curable polymers | **Advantage**<br>–Simple and complex designs can be manufactured; growth factors, proteins, and cells can also be done<br>**Disadvantage**<br>–Only applicable for photopolymers | [21, 22] |

| Technique | Process details | Processed materials for tissue engineering | Advantages and disadvantages | References |
|---|---|---|---|---|
| Fused deposition modeling | Strands of thermoplastic polymers or polymer/ceramic composites extruded through a tip and deposited layer-by-layer | Structural and biopolymers, ceramic-polymer, or metalpolymer composites | **Advantage**<br>–Easy to use and can be used with a large variety of materials<br>**Disadvantage**<br>–Material restriction related to thermoplastic polymers | [23–25] |
| Robotic assisted deposition/robocasting | Direct writing of high solids loaded slurry; good for a variety of ceramics and ceramic-polymer composites | HA/PLA, HA/PCL, and bioactive glass (6P53B)/PCL | **Advantage**<br>–Good for ceramics<br>**Disadvantage**<br>–May not be useful for different materials | [26] |

An American Society for Testing and Materials (ASTM) International committee dedicated to the specification of standards for AM was formed in 2009 [27]. This committee, known as ASTM F42, created a categorization of all 3D printing technologies into seven major groups. Table 3.2 shows the major categories along with the well-known 3D printing technologies that fit within each category.

**Table 3.2** 3D printing techniques and respective vendors

| Category | Commercial 3D printing technologies and vendors |
|---|---|
| Vat photopolymerization | • Stereolithography from 3D Systems<br>• Bioplotters from Envisiontec<br>• Large area maskless photopolymerization from DDM Systems<br>• Lithoz Lithography-Based ceramic manufacturing |
| Material extrusion | • Fused deposition modeling from Stratasys |
| Powder bed fusion | • Selective laser sintering from 3D Systems<br>• Electron beam melting from Arcam AB<br>• Direct metal laser sintering from EOS<br>• Selective laser melting from SLM Solutions |
| Directed energy deposition | • Laser engineered net shaping from Optomec Inc<br>• Direct metal deposition from DM3D<br>• Electron beam welding from Sciaky Inc |
| Material jetting | • Objet from Stratasys<br>• Solidscape 3D printers from Solidscape<br>• Multi-jet Fusion Technology from HP |
| Binder jetting | • ZCorp<br>• ExOne<br>• Voxeljet |
| Sheet lamination | • MCor Technologies |

## 3.3 3D Materials Processing Techniques

In general, there are two modes of processing 3D materials: the extrusion mode and the droplet mode. In the extrusion mode,

the material is extruded out of the nozzle tip under an applied pressure. This mode can basically lay down the material in the form of line structures to create the desired model by moving the nozzle tip over a substrate in the designed path. This process can be repeated layer by layer to develop a freeform fabricated part. In the droplet mode, the material is deposited in the form of droplets that is controlled by using a frequency function and key parameters in the nozzle system settings. The droplet mode can form a structured layer by depositing multiple droplets at desired locations on a substrate. Similarly, this process can be repeated to fabricate a 3D structure. Figure 3.1 shows a schematic diagram of the extrusion and droplet mode for the deposition.

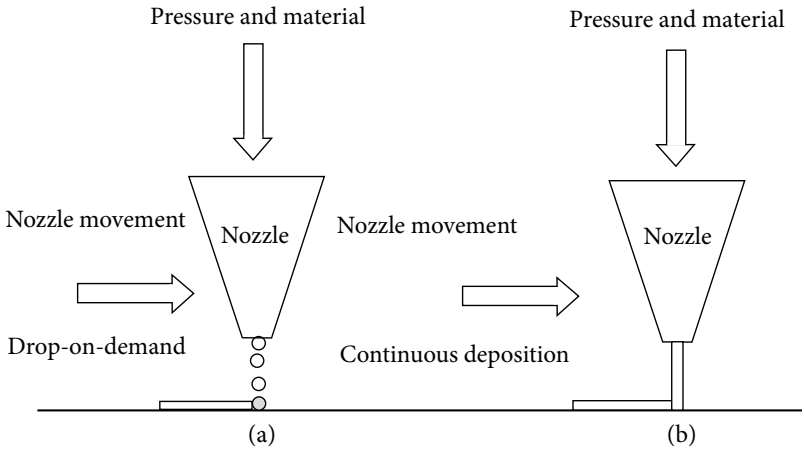


**Figure 3.1** 3D materials processing techniques: (a) extrusion mode and (b) droplet mode.

Each nozzle system is unique in its method of operation, which makes each system have its advantages and limitations over the others. All nozzle systems have a material delivery system. However, the detailed setup for each system is different and the material delivery system parameters such as air pressure are not controlled by in-house software. Characteristics and comparison of the four nozzle systems with their advantages and limitations is shown in Table 3.3.

**Table 3.3** Characteristics and comparison of the four nozzle systems

| | Microvalve nozzle system | | | |
|---|---|---|---|---|
| **Features** | **Pressurized mini extruder** | **Solenoid micro-nozzle** | **Piezoelectric micro-nozzle** | **Pneumatic micro-nozzle** |
| Deposition mode | Continuous | Continuous/droplet | Droplet | Continuous/droplet |
| Operation/control | Rotating screw gear via motor | Frequency pulse of voltage | Frequency pulse of voltage | Frequency pulse of air pressure |
| Key process parameters | Pressure and speed, temperature, material, nozzle diameter, deposition speed | Pressure, frequency pulse, material, nozzle diameter, deposition speed | Pressure, frequency pulse, material, nozzle diameter, deposition speed | Pressure, frequency pulse, material, nozzle diameter, deposition speed |
| Operating range limitations | Screw speed: 1 rps<br>Temperature: 150°C<br>*D*: 7–10 mil | *V*: 40 V(DC)<br>*H*: (1–1,200 Hz)<br>*D*: (30, 50, 70 μm) | *H*: (0–20,000 Hz)<br>*V*: (2100-100)<br>*D*: (30, 50, 70 μm) | *H*: (0.01–14 Hz)<br>Fluid *P*: (0–50 psi)<br>Valve *P*: (70–100 psi) |
| Structure formation | Physical solidification | Physical solidification, chemical reaction | Physical solidification, chemical reaction | Physical solidification, chemical reaction |
| Advantages | Fast solidification, no solvents, strong structure, sterile environment | Room temperature, extrusion and droplet, sterile environment | Room temperature, micro-droplet deposition, controlled volume, sterile environment | Room temperature, high viscosity, extrusion and droplet, sterile environment |
| Disadvantages | Temperature, low melting material | Low viscosity, droplet controllability | Low viscosity, not continuous deposit | Droplet controllability, precision deposition |

More specifically, these methods of processing 3D materials can be divided into two distinct groups based on the step, which defines the shape of each cross section.

As a summary, the first group can be described as a repetitive process of the following:

(i) Apply a "fluid" material as a thin layer on a workpiece (or fluid bed) under construction.
(ii) Induce a selective phase change (solidification) on the current cross section of the work piece.
(iii) Lower the work piece (on a platform) into the fluid bed by one layer thickness; then repeat.

The second group combines the "imaging" step with the addition of the material of a full cross section:

(i) Dispense a liquid or liquefied material as small droplets or filament onto the preceding cross section of the work piece.
(ii) Solidify the new cross section.
(iii) Optionally equalize the new layer to a defined thickness; then repeat.

A third group is the group of "imaging" on a bulk material that uses a (ink) jet technology on a powder bed (ASTM: Binder Jetting) to solidify the loose powder with a liquid solution, which dries or reacts to agglomerate the powder particles at the specified locations of each layer. This method was originally coined with the name "3D printing" by the MIT, but is now used alongside the other techniques with the same designation.

If we look at the second group of technologies where we use addition of the material for each full cross section, without a separate imaging step, we have two major processes, which dominate the market by machine numbers: (Multi)jet printing of reactive resins or molten wax (ASTM: Material Jetting) and extrusion of molten thermoplastics (ASTM: Material Extrusion).

The processes coined as Multijet Modelling or Polyjet use a print head similar to inkjet printers to deposit exactly shaped layers of a photopolymer resin, and normally a support material to partially surround it, which is then immediately cured with a UV lamp. In order to maintain exact layer thickness and compensate for small variations of droplet size, current machines use a

mechanical planarizer, which removes excess material on each pass of the print head.

These machines can process robust resin objects—generally complex acrylate formulations—with high accuracy and resolution, and do not require complex lasers and beam scanners. Some limitations related to materials relate to the viscosity requirements of the jetting process; often the viscosity is reduced by heating the print head and nozzle plate. This heating is also required in machines, which are processing wax materials to produce patterns for investment casting, in jewelry and dental restorations applications notably.

A recent development adds machines with multiple print heads or channels, again similar to color inkjet printers, which can deposit selected mixtures of different materials. Besides a palette of colors, this also allows to assign different material properties, essentially modulus of elasticity, to different regions of a part. It is another step to replace assemblies of several components and fasteners with a single part, which is generally an advantage of additive technologies.

The last technique we look at is based on the original process of FDM and also relies on a rather simple buildup of an essentially standard thermoplastic material (ASTM: Material Extrusion). The concept of melting a "standard" plastic material and extruding it through a thin, heated nozzle seems quite straightforward; the extruded melt can then be spread in a controlled X-Y-movement onto the previous layer of part being built. Obviously, the processing temperature has to be adapted to the specific material and well controlled, and thermal shrinkage after deposition can be reduced by heating the build platform or even the complete build chamber.

Originally developed and implemented as an industrial quality process with larger size machines and a selection of thermoplastic polymers, the scope has now grown into the widest palette of smaller and low-cost machines. Some of these machines are even offered as kits to be built or assembled by the user. Recently, this type of machines have become very popular and also have the largest number manufacturers of quite similar devices, mostly with rather small build volumes of roughly 100 to 200 mm on each side. While the simple machines just have one extrusion head and filament spool, many of the newer developments have

multiple heads and can extrude support and part material for good accuracy and complex shapes, or to combine different colors in a single part.

The most popular polymers in this process are ABS and poly lactide, which is also offered on almost every entry-level printer, but higher-grade machines can also process engineering materials such as polycarbonate, polyamide, or even polyphenyl sulfone. As the starting material in this process already is a thermoplastic polymer, the mechanical properties of parts approach those of traditionally molded or machined products, similar to SLS, but using a significantly simpler machine.

The extrusion-type machines are a specific example that demonstrate the accelerated progress in the development toward the wide availability of 3D printers at affordable cost, relying on the assembly of readily available core components such as precision rails, servo drives, control electronics modules, including computers and software that can handle the complex geometry data. The latter is also essential for the design of the 3D model data based on CAD programs or object scanners; not the least is the declining cost of computers to handle all these data and control the machine components.

Another early method that uses paper or other thin films of material, which are stacked up, bonded together, and cut to shape was called layered object manufacturing (LOM) and has now been revived (ASTM: Sheet Lamination) with the possibility to use standard office paper sheets. Whereas the original version used an IR laser to cut the individual layers, the more recent devices cut the paper with a stencil, and a special option allows printing onto the sheets with an office printer, which then creates fully colored parts. Whereas paper is a well-known standard build material, the pressure- or heat-sensitive adhesives which hold the sheets together are specially developed to fit the process.

It has been observed that a vast choice of 3D printing methods is available, many with a variety of materials to choose from, and generally a large range of possible or preferred applications. Technically the possibilities are almost without limits, and on top of the thousands of applications that are being realized today, there is also a lot of speculation about the imminent replacement of current production technologies with

these new 3D printers. In reality, the majority of users still apply these methods to produce prototypes of all kinds, unique parts and new designs, including architectural models and display objects. There are quite some areas where 3D printing is competitive with the cost and speed required for a specific set of products, and the available materials meet specifications. Today these applications are mostly in the medical field for personalized prostheses, in the aeronautical business for low-volume production of special parts, or complex-shaped tools and fixtures for traditional manufacturing. The benefits are particularly high for complex parts, which can often replace an assembled device with a single print. The user community is constantly expanding the limits toward manufacturing by 3D printing, and with progress on the machine side, improved reliability, build speed, and intuitive user interfaces, the range of these applications keeps growing steadily. Besides that effort, there is a lot of development in materials to expand the scope of manufacturing, notably by the machine manufacturers, independent materials supply companies and at research institutions.

This quest for better materials is also true in the realm of low-cost printers, which are affordable for individuals and schools at higher levels; hobby designers, artists, and researchers can turn their ideas and creations into solid plastic parts. There is notable interest in creating toys, accessories for personal electronics or sometimes even replacements for broken parts.

## 3.4 Biopolymers Used for 3D Printing

Different biopolymers have been studied as materials for the development of devices printed in 3D to be used in medical applications, such as chitosan, alginate, and collagen, among others [2, 28]. Other than biopolymers, poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), polycaprolactone (PCL), and poly-L-lactide acid (PLLA) are the widely used synthetic polymers in the biomedical field [29].

However, not all polymeric materials are applicable and suitable for all manufacturing methods. For example, molding methods are inappropriate for developing medical implants from

hydrogels. Because, the biomaterial cannot be removed without damaging both internal and external architecture, which will most likely cause the implant breakage [29].

Another factor to consider is the degradation rate of the biomaterial, since it is desired that the material degrade once its function is accomplished, which would avoid a second operation on the individuals to remove the implant. In this context, the biodegradation rate of PLLA is too low to match the tissue regeneration process after implantation. Besides, the acidic degradation products of PLLA, such as lactic acid, tend to cause aseptic inflammation in tissue [29]. On the contrary, PCL has the presence of hydrolytic aliphatic–ester bonds, which are unstable. Therefore, its degradation duration can be as long as 24 months for being completely degraded. Thus, PCL is always used to co-polymerize with other materials to have desired degradation properties [1]. So, PCL has a better degradation rate to make long-term implants and controlled-drug-release implants. In this sense, Honda et al. [30] used poly(L-lactide-$\varepsilon$-caprolactone) as a biodegradable sponge and implanted it into a nude mice. After a 4-week experimental process, the result showed that there was the formation of cartilage-like structures in the construct [1].

Additionally, polymers can be chemically modified to match the rate of tissue regeneration and degradation rate of the material as well as to obtain a wide range of properties for biomedical applications, such as mechanical properties, diffusivity, density, and hydrophilicity. In addition, these may have optimal control over specific cellular interactions with the polymer material, whereby cells are comfortable, interacting with proteins that bind to the surface of the material, particularly biopolymers [29].

On the other hand, the combination of more than one biomaterial provides better characteristics than any single type of biomaterial, which in turn leads to the development of composite polymeric materials [29]. In this context, composite polymers as 3D printing materials have been used to improve implant–tissue biocompatibility, i.e., they will not be rejected by the body upon implantation [2]. For example, Inzana et al. [31] developed osseous implants from polymer blends of collagen and Tween 80 using calcium phosphate as a natural filler with

the aim of improving osteointegration and improving the mechanical properties of the implant [31]. However, the development of these materials requires high temperatures that prevent the incorporation of bioactive molecules and drugs during the 3D printing process, which could stimulate bone regeneration or combat infections [31].

The feasibility of 3D printing of composite biopolymers at low temperature has also been demonstrated from low-melting-point matrices [2, 31]. This has allowed the incorporation of drugs, cells, and 3D printing of synthetic or biological polymers such as collagen, thus allowing the development of bioactive implants [2]. Type I collagen is the most abundant structural protein in the human body and is a critical component of bone extracellular matrix, where it plays important roles in this mineralized tissue's strength and toughness. It has been shown that incorporating collagen into mineralized bone cements could enhance their biomechanical properties, as well as their osteoconductive and osteoinductive characteristics. For example, collagen incorporation into hand-mixed calcium phosphate cements has been shown to improve cellular attachment, viability, proliferation, and activity as well as mechanical properties. Advantages of 3D printing over molding or paste injection include patient-specific geometries and controlled spatial patterning of drugs or polymers within the scaffold [31].

## 3.5 Advantages of 3D Printing for Medical Applications

3D printing technology offers significant advantages for medical applications due to the ability to manufacture low-volume or one-of-a-kind parts on-demand based on patient-specific needs. For example, surgical implants are currently manufactured by making a near-net-shape part via forging, casting, or machining operations, followed by specialized surface finishing or treatments for the desired surface, mechanical properties, and aesthetic effects, as shown in Fig. 3.2. These operations require expensive tooling; therefore, patient-specific or one-of-a-kind implants are costly and are rarely used. Other challenges such as difficulty in machining of titanium alloys due to high strength, low modulus of

elasticity, and low thermal conductivity compared with steel makes it more expensive to manufacture patient-specific implants from these materials [32]. Finally, CM technologies can be energy intensive, producing significant amounts of material waste, and are not capable of easily producing implants with functional gradation.

3D printing or AM represents a new option for the production of a variety of biomedical devices such as orthopedic implants. Although AM may require final machining, the AM-based approach allows significant flexibility toward manufacturing customized, low-volume, complex implants. Figure 3.2 compares CM of implants with AM. AM provides geometrical freedom to designers without manufacturing constraints, leading to novel lightweight designs and potentially reduced part counts for medical implants. Specifically for medical implants, AM allows for customized complex shaped functional implants and demand-based manufacturing—which can offer a significant reduction in cost and inventory. Since AM does not require any part specific tooling, cost per part remains constant for AM. However, for CM, there is always a fixed cost for tooling and dies, and therefore, cost per part decreases as the volume of parts increases until it reaches a minimum. Such cost analysis forms the basis and rationale for the use of 3D printing or AM for biomedical devices.

Despite some noteworthy success, the construction of human tissue or entire organs with 3D printing or AM continues to present significant challenges [33–36]. From plastic surgery to cancer treatment and from treatment of birth defects to prosthetics for amputees—all areas of medicine are seeking breakthroughs enabled by 3D printing to enhance quality of life or to help patients live longer.

We present two examples that illustrate future possibilities. Complex craniofacial titanium implants from computed tomography images of a fractured skull, shown in Fig. 3.3, can be fabricated directly using a laser-based AM technology, Laser Engineered Net Shaping. In another example, shown in Fig. 3.4, TE scaffolds for bone regeneration can be produced through SLS of poly(caprolactone), a biocompatible and bioresorbable polymer, and poly(caprolactone)–hydroxyapatite composites [37, 38]. Furthermore, the scaffolds can be produced with a priori designed mechanical properties to match the desired mechanical performance of the target bone tissue.

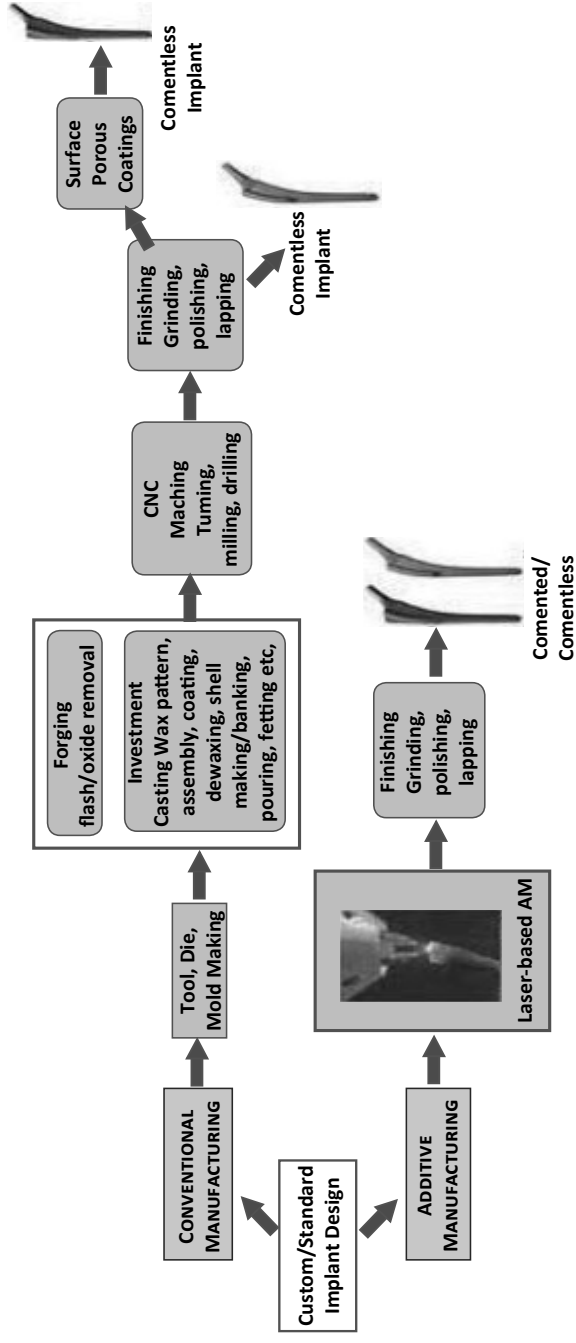


**Figure 3.2** Comparison of additive and conventional manufacturing processes of implants.

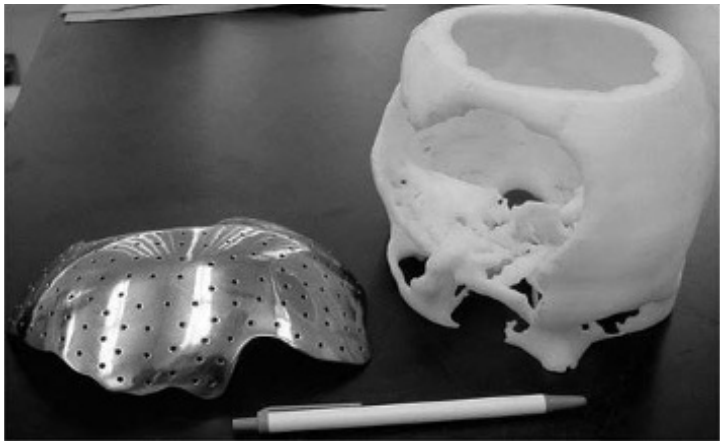

**Figure 3.3** Laser Engineered Net Shaping processed craniofacial Ti implant (left) and fused deposition modeling processed polymer prototype of the skull with large defect (right).

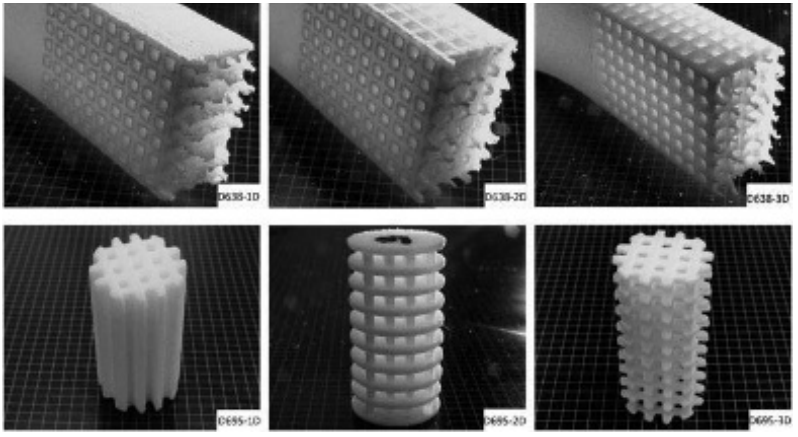

**Figure 3.4** Selective laser sintering-processed poly(caprolactone) tensile specimens shown post-fracture (D638-1D, D638-2D, and D638-3D) and compressive specimens (D695-1D, D695-2D, and D695-3D) based on ASTM D638 and D695 test specimen geometries endowed with 1D, 2D, and 3D orthogonal porous channels (placed on a 2 mm grid).

It is envisioned that application of 3D printing will revolutionize the field of biomedical devices and TE due to its inherent flexibility in manufacturing complex parts using various materials. However, many challenges still remain, due to a lack

of different materials for use in any printer and the inability to manufacture multicomponent structures using commercial printers.

## 3.6 Current Challenges in 3D Printing of Biomaterials

### 3.6.1 Achieving Target Material Properties and Desired Architectures

By virtue of layer-by-layer additive fabrication, it is claimed that 3D printing provides "complexity for free," allowing the physical realization of complex 3D structures endowed with complex internal and external architectures. However, every layer and every interface between adjacent layers provides the opportunity for the introduction of defects during 3D printing that can lead to the failure of the part under the intended application conditions.

Some of the key challenges associated with 3D printing of biomedical implants lie in achieving target mechanical properties, durability, and designed architectures to satisfy both mechanical and functional requirements. This is especially important in load-bearing implants, where mechanical performance and fatigue are critical. 3D printing technologies are being used to produce permanent implants in metals, polymers, and ceramics. The capabilities of these technologies in processing feedstock materials such as titanium, poly(ether ether ketone), and hydroxyapatite need to be well-characterized and documented under diverse conditions both in vitro and in vivo.

The challenges increase when the implants are endowed with intentionally designed or manufacturing-induced porous architectures. The effective mechanical properties and failure modes of such porous architectures need to be well understood and integrated into implant design procedures to avoid undesirable implant failure outcomes. Computational design techniques validated with experimentally measured property data need to be integrated into implant design procedures. Additional challenges lie in the ability of 3D printing technologies

to accurately produce desired porous architectures meeting design intent. Often, the length scales associated with the designed porous architectures (ranging from tens to hundreds of microns) are beyond the resolution capability of the 3D printing technology in use.

Finally, surface finish or surface roughness can be a critical requirement as well. The inherent stair-stepped surface finish from layer-by-layer fabrication or other material consolidation-induced surface roughness artifacts prevalent in 3D printing are often beneficial for cell anchoring, proliferation, and integration, but in other cases, they can be highly detrimental due to the inducement of foreign body reactions or due to the release of particles into regions surrounding the implant. Thus, careful attention has to be paid to understanding surface finish and surface texture requirements as well as choosing appropriate post-processing procedures to attain final desired surfaces in biomaterials fabricated by 3D printing.

### 3.6.2 Clean and Sterile Manufacturing Environments

3D-printed biomaterials are being produced with the intention of use in implants or in laboratory scale studies in bioengineering. In either case, careful attention needs to be paid to the conditions under which the feedstock material is produced, supplied, processed, post-processed, and handled. The scale-up of 3D printing technologies for biomaterials will require careful design of clean manufacturing environments both inside and outside the 3D printing platforms to ensure the avoidance of material contamination and related possible infections. Thus, the design of 3D printing equipment for biomaterials needs to ensure that equipment subsystems can meet the requirements for contamination control, perhaps similar to or even more stringent than those applied in the medical device industry. Furthermore, clean manufacturing environments will need to be designed from the ground up for scale-up manufacturing of 3D-printed biomaterials. New sterilization, packaging, and shipping procedures for 3D-printed biomaterials need to be developed to ensure product integrity at the point of use.

### 3.6.3 Concerns Related to Regulatory Issues

Regulatory issues are specific to a particular country and should be checked for that particular region first. In the United States, medical devices are classified under three categories based on the risk to the patient: Class I, Class II, and Class III. Class I devices are typically the lowest risk (e.g., a tongue depressor). If there is a predicate device, then many devices are classified under Class II, where the new device is substantially equivalent to the previous device, which has already been cleared by the U.S. Food and Drug Administration. Regulatory paths for the Class III or high-risk devices are quite challenging as well as time-consuming. In most cases, regulation follows technology development, and therefore, many times there is a lag in appropriate regulations for certain types of devices.

This is the case for 3D printing and its applications to human health. Although the technology for patient-specific implants is available, no clear regulatory path is established toward immediate utilization of this technology. This is also because the risk associated with the use of this technology is yet to be fully understood and evaluated. A TE graft with tailored porosity and chemistry can be fabricated in hours; however, the scientific factors that need to be verified to confirm that this will perform the same way as before are still evolving. Moreover, the advent of different 3D printing technologies is also making this evaluation more complex. Finally, the needs of specific patients are different. A clear understanding of the biomechanical and biological issues for different parts will eventually help develop regulatory pathways for diverse clinical applications of 3D-printed parts. A logical approach will establish regulatory paths for low-risk devices, such as specialty surgical tools, and then slowly move toward the high-risk devices such as patient-matched implants. It is envisioned that such trends will follow in the coming years in the United States as well as other parts of the world.

### 3.6.4 Material-Specific Machines

Unlike CM processes such as forging or investment casting, many 3D printing processes are different in terms of the materials that can be used and the delivery of materials. For example,

a polymer-based 3D printing process will not work for metals or ceramics and vice versa. This makes process optimization very important for different materials that will be used with a specific printer. The user must know what material will be used and what kind of resolution is needed before selecting a 3D printer. This limitation is the main reason why different companies have multiple 3D printers for a variety of applications.

### 3.6.5 Future Trends

3D printing of multi-material structures is one of the most promising future trends. Different materials at different locations in a structure can offer properties that cannot be achieved using monolithic structures. These materials can only be bonded to each other or alloyed during the part building, allowing for compositional variations in the part. For 3D-printed biomaterials, a simple example can help us understand the power of multi-material 3D printing. For total hip prosthesis, implants are made with either $Ti_6Al_4V$ or CoCrMo alloys. To enhance bone–tissue integration, implants are sometimes coated with porous Ti or Ta metal or calcium phosphate-based ceramics. However, different processing strategies are utilized for the addition of coatings. Using multi-material 3D printing, a calcium phosphate or metal coated hip stem can be directly manufactured from the same machine that can also produce an uncoated sample in the very next run. Therefore, in addition to flexibility in design modifications, the potential of incorporating compositional variations will allow future innovations in advanced materials and structures using 3D printing.

For bioprinting, multi-material structures include cells that can be printed along with organic or inorganic materials to make a fully functional scaffold for TE [39]. Such an approach is gaining considerable attention from a number of researchers, though there are many challenges that need careful attention. For example, cell viability will be key for successful bioprinting operation. Shelf-life of materials with and without cells is another significant issue. Also, due to significant variation in the stiffness of the cells and materials to be deposited, careful process optimization is necessary to build scaffolds that can be used for further in vitro or in vivo analysis.

Another important criterion is vascularization or new blood vessel network formation, commonly known as angiogenesis. Figure 3.5 shows new blood vessel formation in 3D-printed-doped tricalcium phosphate TE scaffolds in a rat distal femur model. 3D-printed TE scaffolds should support angiogenesis for functional tissue formation to enhance healing in vivo [40–46].

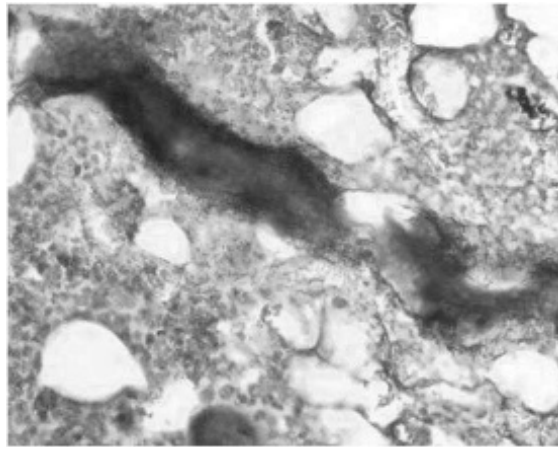

**Figure 3.5** New blood vessel formation in 3D-printed-doped tricalcium phosphate TE scaffolds implanted in a rat distal femur model.

Finally, 3D printing combined with drug or protein delivery is becoming popular and is expected to gain more attention in the future. Drug-/protein-loaded biomaterials with a controlled delivery option can be used to treat many diseases [45]. In particular, specific drug combinations that are patient-matched and unique can be loaded into a single 3D-printed drug delivery device. However, drug–material and drug–drug interactions during 3D printing are complex topics and will require significant process optimization before actual applications can be realized and approved for patient use.

## 3.7 Conclusion

The processing of biopolymers and polymer composites through three-dimensional (3D) printing has been gaining a lot of attention, because of its multiple applications in a wide variety

of industries. In fact, the exploration of the areas of applicability of this technique remains an active area of research. With the latest 3D printers capable of printing materials with a widely contrasting mechanical behavior and with complex geometries at micrometer resolutions, the potential of this technology has grown. This technology now offers the possibility of creating complex topologies with fine features, composed of a multitude of materials with variable mechanical properties on a large scale, thus allowing the manufacture of devices with an unprecedented multifunctional performance [47, 48]. Particularly in medical applications, in the last decade there has been a growing interest in the development of medical systems with bioactive properties, which have been possible thanks to the technological development of 3D printing as well as biopolymers, drugs, natural fillers and implementation in vitro or in vivo of cells in the formulated materials, which have generated a series of implants with outstanding mechanical properties and exceptional biocompatibility, adjusted to the exact dimensions of each implant for each patient. Likewise, because of the greater surface area of these devices, the cells are able to regenerate the tissues at a faster rate, thus allowing the patients to recover quickly, and avoiding a subsequent operation to remove the implant, since these implants are degraded in the time, while this one fulfills the mission for which it was developed. Finally, this type of implant also promises to be a controlled-drug-release device, while the polymer material used is degraded.

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