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# Current Trends in 3D Printing, Bioprosthetics, and Tissue Engineering in Plastic and Reconstructive Surgery

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**Abstract** 3D printing represents a developing technology whose applications in plastic and reconstructive science are only in its dawn, creating devices of limitless customization presenting the possibility for uniquely tailored implantable devices for the individual patient. The advent of tissue engineering presents exciting new possibilities for conventional 3D printing in that novel approaches to reconstruction can be attempted with bioactive molecules and tissues for advanced wound healing, thereby resulting in a dramatic reduction in implantable device morbidity with improved esthetic results. The marriage of these two technologies has resulted in the creation of bioprosthetics, a field in which bioactive molecules are structured into implantable prosthetic devices through 3D printing of cells harvested or engineered in the laboratory. The historical context of conventional 3D printing modalities as well as tissue engineering is presented for discussion in the greater context of the creation of modern bioprosthetics. An outline of common materials, methods, and their utility is also introduced to serve as a framework to better understand the continuing advancements in implantable devices with examples of continuing discoveries discussed where appropriate.

**Keywords** 3D printing · Tissue engineering · Bioprosthetics · Biomaterials · Plastic surgery · Reconstructive surgery

## Introduction

Recent advancements in synthetic and biologic prostheses have been accompanied by continuing development of novel manufacturing technologies. Among these is three-dimensional (3D) printing, which in recent years has gained momentum in several medical disciplines including plastic and reconstructive surgery. Through the production of fully actualized constructs, 3D printing provides an array of tools that can be tailored to the needs of the individual patient in a fashion heretofore impractical or impossible utilizing previous methodologies. In combination with the developing field of tissue engineering, these new methods of manufacture have paved the way for further scientific breakthroughs in advanced medical prostheses, with implantable devices now produced containing partially or completely biologic components that result in fewer complications and offer improved clinical outcomes (Fig. 1).

The general advantages of 3D printing are owed in large part to the ability of device customization and rapid delivery time, with specific advantages determined by the type of material used for printing. Individualization allows for accurate reproduction of patient-specific anatomy either for surgical planning or didactic purposes and can safely be implanted into the patient. These devices then serve as a scaffold, bridge, or internal splint without equal in assisting the healing process. Bioprosthetics are unique among 3D

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constructs in that biological materials eventually incorporate or degrade while in the patient. Due in large part to the production of immortalized normal cells and the birth of tissue engineering, complex tissues can be fabricated to perform specific biochemical functions to supplement or substitute specific structures or organs. 3D printing, tissue engineering, and bioprosthetics lie at the intersection of cutting-edge technology and clinical science, offering state-of-the-art technology that reduces donor site morbidity while affording functionality previously thought impossible through alternative means as traditional manufacturing due to the implied cost, time, and technical modifications. Whereas 3D printing cost remains constant with each manufactured piece that can be specifically modified for printing, traditional manufacturing requires machinery modifications for each new, patient-specific modification. 3D printing also reduces delivery time, and if 3D printing is performed in or near the location where the product is to be utilized, multiple prototypes can be printed, trialed, and modified on demand.

## 3D Printing

3D printing technology, described elsewhere as additive manufacturing (AM), rapid prototyping (RP), or solid free-form (SFF) technology encompasses a family of technologies that fabricate physical structures from two-dimensional (2D) computerized instructions. Utilizing materials as diverse as plastic, metal, ceramics, or biomaterials, structures are created through the successive deposition of material layers in a stepwise fashion as determined by the computerized blueprints programmed by the user [1•]. The end result is a three-dimensional construct whose utility is virtually limitless (Fig. 2).

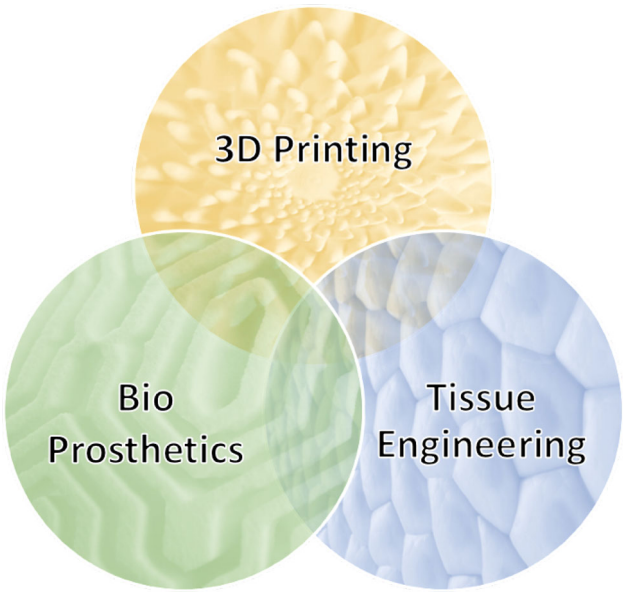


**Fig. 1** Interrelatedness of 3D printing, tissue engineering, and bioprosthetics in forming the next generation of implantable devices. 3D printed scaffolds are lined with tissue-engineered cells creating the next generation of implantable prosthetics—bioprosthetics

Initial efforts to utilize 3D printing primarily focused on the manufacture of objects identical to those produced through traditional assembly processes [2]. When introduced to the medical sciences, the applications for 3D printing grew rapidly, including the creation of anatomical teaching models and preoperative planning devices (Fig. 3), tissue and organ fabrication for transplantation, custom prosthetic and bioprosthetic implants, and the development of novel pharmaceuticals and drug delivery systems [3•, 4•]. Compared to devices manufactured through alternative means, 3D printing affords the clinician the unique opportunity to quickly and efficiently produce products specifically tailored to the individual therapeutic needs of any patient [3•, 5, 6].

Recent advancements in the field of tissue engineering have made possible the use of 3D printing technology to fashion components out of biological materials. This subspecialty of 3D printing, often referred to as bioprinting, has permitted the creation of hybrid structures consisting of organic tissue blended with synthetic materials. Such constructs have included bone and skin in combination with synthetic mesh to produce subtotal and total organs of predetermined shape and size specifically tailored to the needs of target recipients [7•, 8]. Bioprinting offers highly precise computer-assisted cell placement capable of regulating the speed at which cells are deposited, the volume and diameter of the printed cells with detailed resolution [7•]. In addition, the nature of the 3D bioprinting data files allows rapid access to researchers and surgeons as they are part of an open-source database readily available for tissue engineering, repair, or replacement [1•, 9].

To date, several 3D printing methods exist, utilizing different printer technologies, speeds, and materials (Table 1) [10, 11]. Of these, there exist five main subdivisions of 3D printing used in plastic and reconstructive surgery:

(1) Stereolithography (SLA) was the first 3D printing technology used in reconstructive surgery. The process involves the deposition of a photopolymer or epoxy resin which is then cured by low-power UV laser [10, 12]. Common photo-crosslinked macromolecules used as scaffolds in SLA 3D tissue engineering include poly(propylene fumarate) (PPF), photocurable synthesized polymer variations of poly(ethylene glycol)/poly(D,L-lactide) (PEG-PL) hydrogel, and gelatin methacrylate (GelMA). These

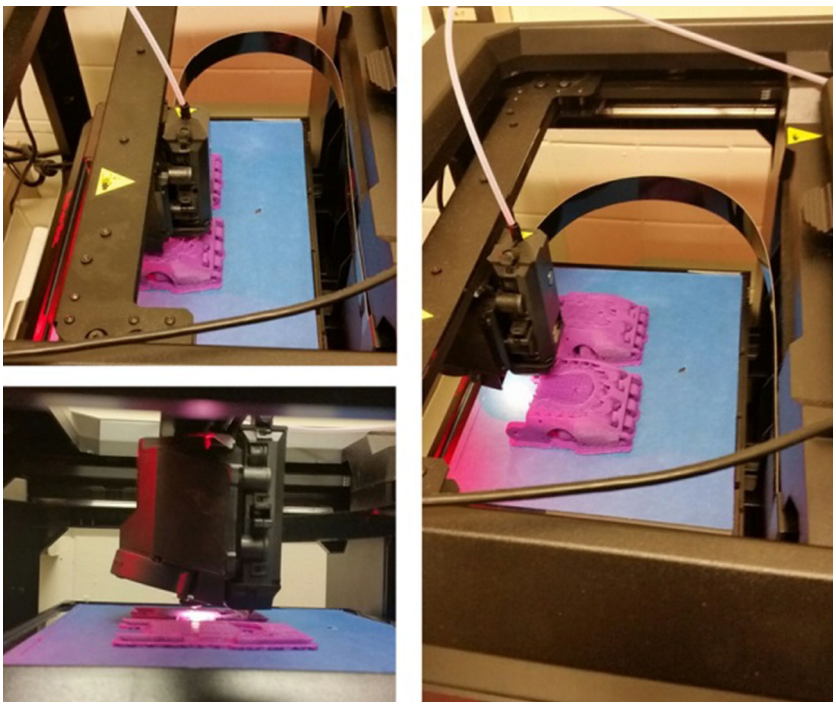

**Fig. 2** 3D printer constructing pediatric hand prosthesis in different stages of printing

**Fig. 3** Didactic applications of 3D printing. Reconstruction of various pediatric congenital craniofacial deformities derived from clinical 2D imaging. Clinicians are able to manipulate constructs previously relegated to reproductions in print media, affording greater understanding and appreciation for anomalous anatomy

materials have been utilized for a number of research and clinical applications. Among these, PPF has been successfully used in rabbit cranial reconstruction; PEG-PL has been proven to promote human mesenchymal stem cell adherence and proliferation; GelMA demonstrates high pore interconnectivity useful in the uniform distribution and proliferation of human umbilical vein endothelial cells in scaffolding [13•, 14, 15]. SLA has proven to be of exceptional value in the creation of anatomical models for presurgical planning and medical device modeling [16]. Advantages to SLA include extremely high product resolution up to approximately 1.2 μm and the capacity to fabricate shapes with high degree of intricacy, although unpolymerized resin must be removed manually. Key disadvantages which potentially limit the use of SLA are that only a few biocompatible materials are available, with those available having poor mechanical properties. Furthermore, the cytotoxicity of some photoinitiators proves a challenge for some clinical applications and the need to incorporate support structures into the computer model to assist the printing process can present difficulty when trying to remove them upon printing completion [17••].

(2) MultiJet Modeling (MJM) printing, MultiJet Printing, or Poly Jet Technology resembles SLA but with the

**Table 1** Comparison of advantages, disadvantages, and utility of 3D printing methods used in plastic and reconstructive surgery

| 3D Printing method | Advantages | Disadvantages | Applications[†] |
|---|---|---|---|
| Stereolithography (SLA) | High resolution<br>Able to fabricate complex structures | Few biocompatible materials<br>Need for photoinitiators that may be cytotoxic | Didactic and surgical planning<br>Scaffold for bony reconstructions |
| MultiJet modeling (MJM) | Immediately cured by UV (faster) | Cost<br>Lower resolution compared to other technologies | Scaffolds for bony reconstruction, (currently cost prohibitive) |
| Selective laser sintering (SLS) | Smooth surface<br>High resolution[‡]<br>Powder can be reused<br>Post-fabrication treatment can improve characteristics of final product | High temperature for laser<br>Limited material library<br>Fusing of neighboring powder particles | Implants for bone regeneration |
| Binder Jet technique (BJT) | Inexpensive<br>Variety of materials can be used | Poor strength<br>Poor finish | Scaffolds for cartilage and bone growth |
| Fused deposition modeling (FDM) | Inexpensive<br>Good mechanical strength | High temperatures preclude ability to add living cells during extrusion process<br>Mono-material structures | Scaffolds for cartilage growth<br>Drug delivery systems |

[†] These applications are a small representation of some of the experimental and clinical uses of these 3D printing methods related to plastic and reconstructive surgery and are by no means exhaustive

[‡] High resolution can be negated if heat diffusion occurs, fusing neighboring powder particles

addition of multiple printer heads. In contrast to SLA, the liquid photopolymer is immediately cured by UV light, avoiding the long post-processing time in the UV chamber [10, 18]. Product resolution is lower compared to SLA at approximately 16 μm but with the added advantage that different materials can be printed and can be used for anatomical modeling. Unfortunately, to date MJM remains cost prohibitive for single-patient use, making it more appropriate for large-scale production.

3) Selective laser sintering (SLS) consists of sequential layering of a laser-sintered reusable powder with thermoplastic, metal, glass, or ceramic materials [10, 19, 20]. It produces objects with smooth surfaces and a high resolution limited to approximately 10 μm. The maximum resolution is primarily dependent upon the size of the powder particles, the laser beam diameter, and the heat transferred to the powder. Materials used in SLS 3D printing to fabricate scaffolds for tissue engineering include PCL polymer, polyether ketone, hydroxyapatite (HA), and biocompatible polymers such as polyetheretherketone (PEEK), poly(vinyl alcohol) (PVA), polycaprolactone (PCL), and poly (L-lactic acid) (PLLA) [21, 22]. SLS affords the unique ability to fabricate implants for bone regeneration with the advantage of creating complex structures that once cured are of considerable strength (Fig. 4) [23]. Unfortunately, due to the high laser temperature required during the curing process, a limited variety of materials can be used. This combined with low resolution due to heat diffusion of the laser beam and an undesired fusing of neighboring powder particles limits functional utility.

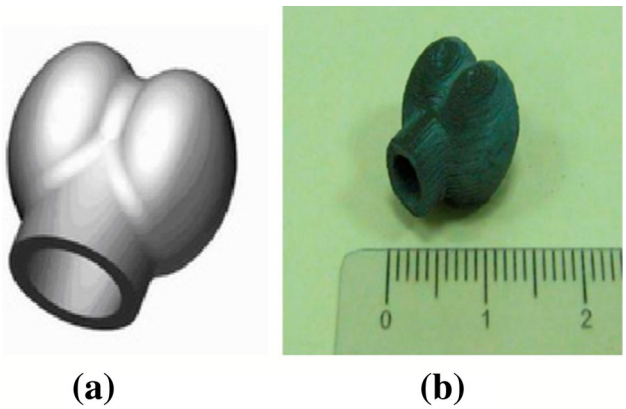


**Fig. 4** Biomedical titanium bone scaffolds for implantation. The use of medical-grade metal in prosthetics has been thoroughly established as an efficacious means of bone reconstruction. The above titanium bone scaffold was obtained by selective laser sintering whose parameters were set to a layer thickness of 100 mm, laser power 15 W, scan velocity 100 mm/s, hatching space 0.1 mm, energy density 1.5 J/mm$^2$, laser beam size 0.2 mm, and laser frequency 16 kHz. **a** Computerized representation of the proposed titanium construct generated through CAD. **b** Completed bone scaffold prosthesis. Reproduced with permission from Liu et al.[23]

(4) Binder Jet Technique (BJT) or Powder Bed Technique fabricates 3D structures by inkjet printing with liquid binding solution selectively deposited onto powder bed particles. The process is inexpensive although objects have poor strength and poor surface

finishing when compared to SLA or SLS. A variety of materials can be used, among which are calcium polyphosphate, PVA, HA, and tricalcium phosphate [25, 26]. Ceramics have also been used with this technique to further serve as a scaffold for cartilage and bone growth [27, 28]. The main advantages of BJT 3D printing are its extensive range of available materials, the direct control over pore size at the microstructure level, and fine control of the shape macroarchitecture. Disadvantages include low resolution, limitation of layer thickness greater than the porogen particle, low product strength, limitation of organic solvents, and difficulty in removing unwanted powder [17••].

(5) Fused deposition modeling (FDM) deposits thermoplastic material of low melting temperature along a two-dimensional X–Y plane with biocompatible polymers used to fabricate scaffolds [29]. Compared to SLA, FDM is faster, more accurate, and less expensive. Cohen et al. reports using FDM to fabricate models to guide contouring of a mandibular reconstruction, thereby shortening operating time, blood loss, and exposure time to anesthesia [30]. The main biocompatible polymers used to fabricate scaffolds are L-lactide/ε-caprolactone (PLC) and poly(ε-caprolactone)/bioactive glass (PCL/BAG) which is highly biocompatible with fibroblasts [31]. Additional work utilizing FDM printing has yielded promising results for future work. In vitro highly porous lactide-co-glycolide (PLGA) scaffolds fabricated with FDM and modified with Type II collagen scaffolding show fiber spacing comparable to native articular cartilage in porcine models with well-distributed chondrocyte and neocartilage formation around the scaffolds [32•]. PCL–tricalcium phosphate (TCP) mesh has been fabricated to locally deliver gentamicin, proving to be effective in eliminating bacteria with low cytotoxicity [4]. In vivo studies utilizing poly(D,L-lactide:glycolide) (DL-PLGA) and β-tricalcium phosphate (β-TCP) scaffolds coated with HA implanted into rabbit femoral unicortical bone defects resulted in complete scaffold integration into the host bone [33].

FDM provides high porosity due to its unique lay-down pattern and offers good mechanical strength. This technology is of limited bioprosthetic utility in that no living cell or temperature-sensitive biological material can be introduced into the scaffold during extrusion due to high production temperatures. Application is further limited by the fact that structures are commonly mono-colored and mono-material [10, 17••].

Recently, four-dimensional (4D) printing has entered medical study for the purpose of movement analysis, with the fourth dimension consisting of time. In one study utilizing 4D computed tomography, scans of thumb movement were obtained and printed with conventional 3D techniques, providing spatiotemporal anatomical details of significant clinical utility for the preoperative planning of procedures involving highly mobile areas [34].

## Bioprostheses

The term "bioprosthetic" was initially used to refer to heart valves manufactured from biomaterials that were constructed to be durable and permanent. It was presumed that these devices would potentially avoid the clinical complications and failures associated with mechanical heart valves, thereby reducing recipient morbidity and mortality [35]. These valves were first made from pure homograft and later xenograft. Although modern bioprosthetic materials are derived from animal or human tissue, some native biological properties and extracellular matrix structure of the original tissue are preserved [36, 37]. Bioprosthetic materials act first as a mechanical support to permanent mesh implants, then serve as a biological scaffold to be remodeled within the host tissue once implantation occurs [38]. This unique element of host remodeling is among the reasons why bioprosthetic materials have an increased rate of prosthetic incorporation, affording better clinical outcomes in recipients compared to conventional synthetic implants.

Collagen for use in bioprostheses is harvested from human, porcine, or bovine models due to their high homology with human tissue and is mainly used as the framework upon which bioprosthetics are built. This is in large part due to its capacity to form intricate cross-linking, affording an increased strength, resistance, and stability to the prosthetic by increasing the collagen intra- and interfibrillary bonds. Chemical treatment with formaldehyde followed by glutaraldehyde can be used to further "improve" collagen, forming a highly stable lattice cross-linking adjacent collagen molecules [35]. This technique is of limited utility as host tissue inflammation and calcification can occur, specifically in soft tissue implants [39]. The characteristic of the cross-linking depends on the concentration, solvents, temperature, and duration of the compounds used. Furthermore, acyl azide and carbodiimides present from the conversion of the aspartic acid and glutamic acids within collagen produce smaller cross-linking distance, which allows better prosthetic implantation [35].

The organic biomaterials utilized in bioprosthetics are either degradable or become incorporated into the host tissue. When compared to synthetic materials, this results in a reduction of body rejection while promoting

integration and vascularization with improved healing [40, 41••]. At present, research is focused on developing custom biomaterials, tailoring such characteristics as pore size, shape, porosity, spatial distribution, tension, and mechanical strength to create materials better suited for cellular attachment, proliferation, and differentiation in host tissue [42]. However, as the strength of the material increases, vascularization capacity of the bioimplant decreases, presenting a unique challenge to bioengineers [35].

Chronic wound healing presents a novel area of study for the application of bioprosthetic research. Both cellular and acellular materials have been developed for the treatment of diabetic, chronic, and burn wounds. Specifically, in burn reconstruction bioprosthetic skin grafts have proven useful in replacing dermal layers of difficult-to-treat burn reconstructions [43–46]. Banyard et al. completed a thorough review of the literature on this subject, determining that the dermal matrix is among the most significant factors determining burn wound healing. Through the application of these novel skin grafts, Banyard concludes that there are significant reductions in healing time, esthetic need, and scar contracture with greater preservation of skin elasticity [44]. Although an active area of ongoing research, to date epidermal layer grafts have not yet been developed.

O' Brien et al. performed histology, immunohistochemistry, and mechanical testing of a 1 × 6 cm section of a Permacol$^{TM}$ bioprosthesis originally placed for repair of an abdominal wall hernia that was obtained during an incision and drainage of a fluid collection posterior to the Permacol$^{TM}$. Testing showed that the implant maintained durability, allowed vascular ingrowth, and demonstrated integration with human collagen and elastin [47].

Ceramics have been used for surgical implantation due to its high degree of biocompatibility and inert chemistry combined with relatively high strength and low thermal and electrical conductivity. However, ceramics possess low ductility and a high degree of brittleness which limit their clinical utility in bioprosthetics [48].

Currently, a diverse number of biomaterials are derived from multiple different sources, including human and animal tissues, naturally occurring organic materials, synthetic polymers, and metals (Table 2). Materials vary in degree of bioreactivity, with each offering its own set of advantages and disadvantages based on the physical properties of the material. These must be considered when planning the form and function of a bioimplant. For example, in bone reconstruction a bioimplant would need a modulus of elasticity comparable to bone in order to maintain uniform stress distribution while possessing high tensile and compressive strengths resistant to shear and fatigue forces to prevent fractures.

Metals are unique among materials utilized for bioprosthetics in that they are highly resistant to deformation and corrosion while remaining easy to process and sterilize and are therefore commonly used in implantable devices. They are either biotolerant or in the instance of Titanium (Ti) and its alloys even bioinert. Titanium has a high degree of passivity and can both be rapidly formed and made of controlled thickness. Titanium is very resistant to corrosion by forming a thin oxide film on itself; even if the film is damaged, the metal can repair itself in the presence of oxygen. The thickness of this layer can be chemically increased. This also makes it resistant to chemical degradation. Titanium serves as an active catalyst for a number of chemical reactions and has modulus of elasticity compatible with that of bone. Titanium is therefore the material of choice for dental and intraosseous implants [49, 50]. While offering no specific functional deficiency, the use of titanium in clinical applications is limited to cosmetic concerns of the patient due to the dark gray color of the metal. Recently, titanium–zirconium alloys with 13–17 % zirconium (TiZr1317) have been shown to have increased elongation and fatigue strength than pure elemental Ti while maintaining growth of osteoblasts in experimental models. The result is a thinner implantable device which can be subjected to higher strains when TiZr1317 is utilized, as long as the material shows a similar biocompatibility with pure Titanium [51].

## Tissue Engineering

Tissue engineering is a new field of study principally focused on the repair or replacement of bone, cartilage, skin, muscle, blood vessels, and other tissues through cellular manipulation [52]. Continued advancement in the fields of biomaterials, stem cell research, biomimetics, and cellular growth, and differentiation factors have made possible the construction of extracellular scaffolds and matrices impregnated with cells and biologically active

**Table 2** Common materials utilized in bioprosthetics

| | |
|---|---|
| Bioactive | Hydroxyapatite, tricalcium phosphate, bioglass, carbon–silicon |
| Biotolerant | *Synthetic polymer* Polyethylene, polyamide, polymethylmethacrylate, polytetrafluroethylene, polyurethane |
| | *Metal* Gold, cobalt–chromium alloys, stainless steel, niobium, tantalum |
| Bioinert | *Ceramic* Aluminum oxide, zirconium oxide |
| | *Metal* Commercially pure titanium, titanium alloy (Ti-6AL-4U) |

molecules which restore or establish normal function [53]. Modern tissue engineering owes its successes in large part to the pioneering work at the end of the last century. Initially unsuccessful attempts had been made as early as 1994, when cartilage was synthesized using biodegradable synthetic polymers as vehicles for transplanted bovine articular chondrocytes [54]. Eventually through telomere extension via telomerase-enriched cellular clone lineages, Geron Corporation was able to produce immortalized cells with reduced cell senescence which has served as the groundwork for current cellular and tissue production [55].

Autologous cells are principally used in tissue engineering projects at present although these are usually very limited and in many cases unavailable due to comorbidities such as genetic disease, extreme age, or severe burn injury. Additional difficulties presented with autologous cells manifest in the culturing process which is time intensive and prohibitive to emergent procedures. The use of mesenchymal stem cells with near totipotency allows for the engineer to prepare tissues as diverse as bone, cartilage, fat, or even nerve to provide "off-the-self" organs grown in vitro. This technology therefore offers an alternative to life-long immunosuppressive drugs for transplant patients in a post-antibiotic age [56].

Several methods have been described for preparing porous 3D structures to be used as tissue engineering scaffolds for attachment and subsequent cell differentiation. Among these are as follows:

(1) Nanofiber (peptide) self-assembly fabricates biomaterials using hydrogel scaffolds with nanoscale porous structures. In recent years, new synthetic nanomaterials have been used as scaffolds to create biomimetic micro-environments resulting in the formation of carbon nanotubes. These nanotubes possess increased tensile strength and enhanced conductivity, and contain synthetic nanospheres that allow controlled release of morphogens and the magnetic nanoparticles necessary for vascular tissue engineering [56–60]. Other materials such as nanotitanite wires improve matrix interaction and increases cell adhesion, while gold nanowires provide control over biomolecular localization within the scaffold. [61, 62]
(2) Textile technologies are methods based on the fabrication of non-woven meshes consisting of different biocompatible and biodegradable polymers such as non-woven poly(lactide-*co*-glycolide) (PLGA) [63]. These methods are limited by difficulties in obtaining high porosity and difficulty in standardizing pore size.
(3) Solvent casting and particulate leaching (SCPL) creates structures with regular porosity by dissolving a polymer in an organic solvent which is then cast into a mold filled with porogen particles to produce the scaffold. These porogen particles can be made of sodium chloride, crystals of saccharose, gelatin, or paraffin spheres. After solvent evaporation, the composite material is dissolved, leaving a porous structure [64]. Drawbacks to SCPL include difficulties in managing pore size and thickness of the structure.
(4) Gas foaming is a process where gas is used as a porogen, bypassing the need for organic solvents and solid porogens [65]. Structures are placed in a heated mold under highly pressurized $CO_2$ for several days. As the chamber depressurizes to atmospheric pressure, porous structures are formed. This technique is limited to only high-temperature polymer scaffold.
(5) Emulsification/freeze-drying adds water to a dissolved porogen polymer, forming an emulsion that is then casted into a mold and immersed in liquid nitrogen. The frozen emulsion is then freeze-dried, creating a porous solid structure. This technique is quite rapid but requires the use of solvents. The porous size is small, and about 85 and 325 μm of collagen glycosaminoglycan scaffolds are produced [66•].

6. Electrospinning is the process of introducing electrical current into a charged solution, ejecting very fine micro- and nanofibers separated by electrostatic repulsion [67]. The main advantage of electrospinning is the low cost of the technology and its relative ease of use. Electrospinning only requires a 30 kV electrical supply, syringe, flat-tip needle, and a collector. For these reasons, it is the most commonly used method to fabricate scaffolds. However, there is often irregularity in the size of pores produced. This technique is capable of producing nanofibrous scaffolds from native polymers such as collagen and elastin, shown to mimic the structure and morphology of native extracellular matrix (Fig. 5) [68••].
7. Computer-assisted design/manufacturing (CAD/CAM) technologies consist of computer assistance to produce 3D scaffolds of desired porosity. The matrix is manufactured via inkjet printing, fused deposition modeling, or by solid free-form fabrication [69–71]
8. Laser-assisted BioPrinting (LaBP) is a method which allows the positioning of different cell types or biomaterials in a defined 3D scaffold. LaBP consists of two coplanar glass slides, with an upper "donor slide" and a lower 'collector slide." The donor slide contains a gold light-absorbing layer and a layer of biomaterials and cells which is then exposed to laser. A gas pressure is generated by the heat of the laser hitting the gold layer, ejecting the cells to the hydrogel-coated collector slide where they are secured in a humid environment. Utilizing this method, Koch

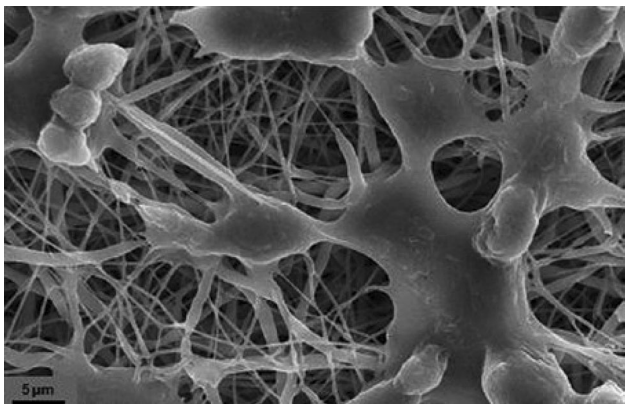


**Fig. 5** Electron micrograph of polycaprolactone fiber mesh. Polycaprolactone mesh is capable of serving as a nanofibrous lattice generated from native polymers such as collagen and elastin. The resulting structure is capable of mimicking the shape and morphology of nascent extracellular matrix. Reproduced with permission from Coutinho et al. [68••]

et al. successfully fabricated human mesenchymal stem cell tissue constructs from skin fibroblasts and keratinocytes for in vivo implantation in animal models [72•].

## Developing Trends in 3D Printing, Bioprosthesis, and Tissue Engineering in Plastic and Reconstructive Surgery

Despite the growing number of applications for 3D printing in medicine, it is only used in a small percentage of clinical reconstructions. This is expected to change in the coming years as the necessary equipment becomes less expensive, and printing software is made more accessible. Whereas clinical applications for 3D printing first began in the early 2000s with the construction of dental implants and prostheses, today plastic and reconstructive medicine has implemented 3D printing for use in facial transplantation and postoperative craniofacial implants [3•, 10].

## Craniofacial Reconstruction

Craniofacial plastic surgery is among one of the fastest growing fields of medicine to make use of 3D printing. A recent case series by Choi et al. highlights experiences with over 500 craniofacial cases utilizing 3D printing in the past decade encompassing maxillary, orthognathic, orbital wall, and cranial reconstruction with tremendous degrees of success both clinically and cosmetically [73]. Similarly, the work of D'Urso et al. reports efficacious use of 3D SLA in the manufacture of individualized cranioplastic implants custom tailored to patient specifications based on CT imaging of 30 cranioplasty patients. Through mirroring and interpolation, master implants were designed and fabricated to produce a mold used to cast the patient-specific acrylic implants. This technique reduced surgery time and produced sufficient cosmetic results. The downside to the use of this technology included additional costs to the patient combined with computer CT data processing time in excess of 2 h and a manufacture time of at least 2 days [74]. Further work into the application of synthetic carbon fiber-reinforced polymers (CFRP) for cranial implantation has also been attempted using 3D SLA and template modeling to repair extensive cranial defects [75, 76]. Individualized reconstructions of patient skulls using CFRP acquired through CT data allowed for the production of wax prostheses and ultimately the creation of cranial implants from CFRP molds.

Recently, a topology optimization method was developed for designing patient-specific craniofacial implants which were embedded directly into computer-generated patient skull models, bypassing cadaveric or patient trial and error in order to restore the form and function of mastication. The 3D construct of the complete skull model with the implant was prepared by applying digital image correlation (DIC) to compare the finite element model of patient-specific craniofacial implants with data obtained during simulated mastication. This computational and experimental approach for the design of patient-specific implants has shown to be a viable technique for mid-face craniofacial reconstruction [77]. Precise mandibular reconstruction is paramount to ultimately allow dental implant placement, proper articulation, masticatory function, and esthetic results.

CAD/CAM-derived 3D Ti mesh implants have been prepared for patients requiring bifrontal cranioplasties due to skull defects. No major postoperative complications were detected, demonstrating that CAD/CAM 3D Ti mesh implant is an encouraging technique for large skull defects due to its safety, practicality, and surgical stability. However, as there are large differences in mechanical properties between Ti cranioplasties and bone grafts, future research will likely target the development of new porous metal–polymer hybrid implants with properties close to bone and that resist mechanical masticatory stress [78].

Maxillofacial reconstruction has also been completed utilizing assorted 3D printing technologies. Artificial maxillofacial bone implants have been fabricated from αTCP powder using an inkjet printer by Saijo et al. in 2009 (Fig. 6). This was the first time artificial bone implants for maxillofacial deformity corrections were fabricated using 3D technology. The main advantages were minimal size and shape adjustments which reduced surgical time, and postoperative evaluation showed that the implants were

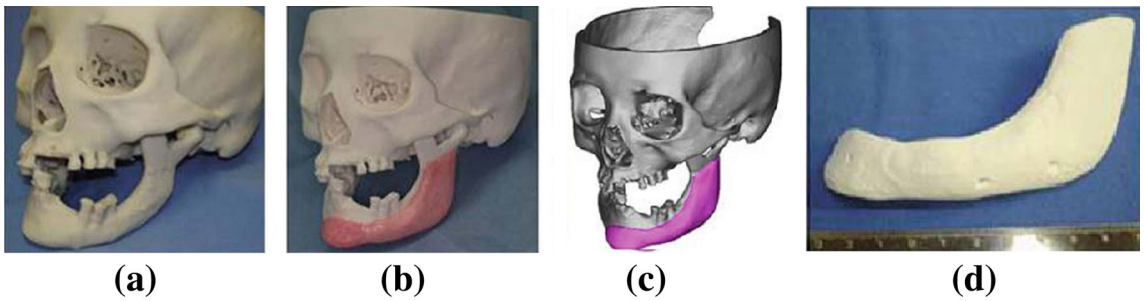


**Fig. 6** Simulation using three-dimensional (3D) plaster model. **a** Preoperative 3D plaster model showing the deformity of transplanted autograft in the left lower jaw. **b** The design of an artificial bone created on the 3D plaster model with special radiopaque wax (*pink*) by the surgical operator. **c** Extraction of the CAD data of the created artificial bone (*red*) based on computed tomography (CT) image. **d** Macroscopic image of the inkjet-printed custom-made artificial bone (IPCAB). Reproduced with permission from Saijo et al. [94]

biocompatible and partially osteoconductive as demonstrated by CT scan [79•]. This technique was expanded upon by Klammert et al. in 2010 to fabricate craniofacial implants, showing that 3D printing of calcium phosphate serves as a biodegradable synthetic patient-specific craniofacial bone replacement [80]. In addition to calcium phosphate synthetic implants, nanoscale biomimetic hydroxyapatite/polyamide (n-HA/PA) scaffold has been used as a mandibular condyle implant by means of CAD/CAM 3D printing fabrication. In this instance, the patient had previously undergone mandibular angle reduction with malocclusion, deviated mouth, hemifacial collapse, and masticatory problems. Augmentation via n-HA/PA resulted in an improvement in appearance and temporomandibular joint function [81]. 3D printing-assisted mandibular reconstruction has increasingly become so common among craniofacial surgeons as to warrant the formation of guidelines for 3D printer-generated osteotomies. These osteotomies can also act as splints to precisely reposition bone and direct plate placement, thereby improving accuracy in reconstruction (Fig. 7) [82•, 83]

Nasal reconstruction has also been performed using 3D printing molds constructed from CT scans of cadaveric cartilage. Human chondrocytes from nasal cartilage were mixed with poly(glycolic acid) poly-L-lactic acid and cultured in vitro to then be implanted subcutaneously into nude mice. The histologic analysis showed that both the cell and tissue of engineered cartilage were similar to those of native lower lateral cartilage, concluding that 3D printing and tissue engineering allow the construction of 3D shapes of human nasal alar cartilage and may perhaps be approaching clinical use in the coming years [84].

Bos et al. developed a multidisciplinary approach to ear reconstruction utilizing cadaveric ears for soft tissue dissection and formation of customizable 3D printing of ear implants via STL methodology [85]. To date, this represents one of the only peer-reviewed studies in the literature regarding auricular reconstruction utilizing 3D printing techniques.

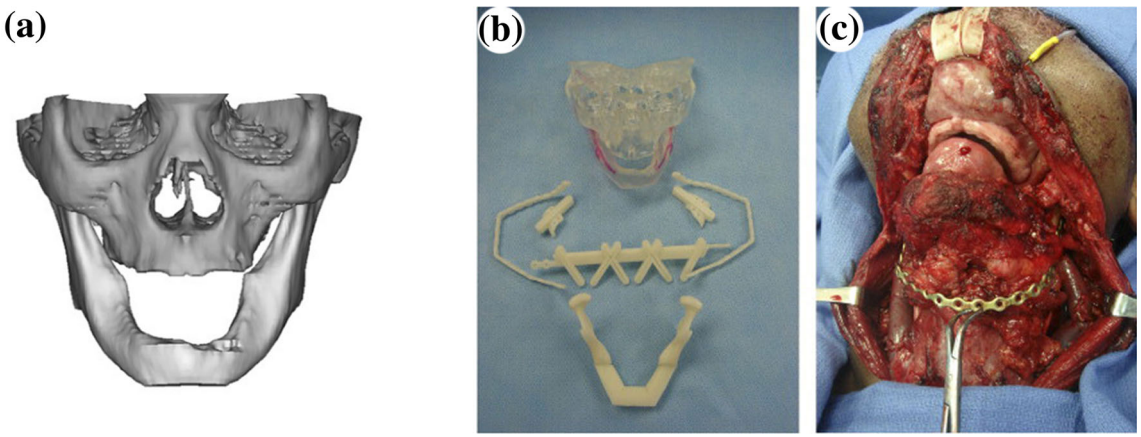


**Fig. 7** Stereolithographic model for maxillofacial reconstruction. **a** Preoperative 3D CT reconstruction. **b** Model of craniofacial skeleton, planned neomandible, plate template, and cutting guides. **c** Cutting guides fixed to mandible before resection. Image modified and reproduced with permission from Hirsch et al. [83]

## Other Clinical Applications

Advancements in the area of preoperative planning have also been of note in recent years. 3D modeling of ankle soft tissue wounds have been repaired by superimposing left and right ankle imaging to produce a 3D construct of a mirror image of the defect, aiding in surgical planning of soft tissue wound coverage [86]. 3D reproduction of the internal mammary artery perforator from cadaver models using composite powder printing process has been accomplished by applying a modified lead oxide technique [87]. Also haptic modeling of a subluxated first carpometacarpal joint has been performed, establishing the relationship between the trapezium and the first metacarpal. Manipulation of the reconstructed model familiarized the surgical team prior to operation [10].

In addition to preoperative planning, 3D printing, bioprosthetics, and tissue engineering are becoming useful for intraoperative guidance. Application of 4D printing has allowed for the analysis of the positional transition during thumb movements, offering valuable spatiotemporal anatomical information [34]. A bone reduction clamp for finger fractures has been manufactured using downloadable software to fabricate a 3D model of the device [88]. Currently, open-source downloadable ready-to-print models of laboratory instruments are available under the format of "open labware." [9]

## Organ Production for Transplantation

The shortage of organs and tissue for human transplantation is a major issue in medicine potentially alleviated by thermal inkjet 3D bioprinting which has widened the possibilities to new sources of transplantable tissues. Inkjet 3D-printed mammalian ovary CHO-S cells transfected with plasmid DNA by co-printing potentially allows clinicians to implant tissues biocompatible for reconstruction [89]. Depending on the tissue type needed, vascular or nerve cells can be added to the organ during assembly. Bioprinting is able to fabricate tissue from "bioink" ejected layer by layer to form a 3D living structure printed from CT or MRI scanned images [90]. Although thermal inkjet printers use temperatures in excess of 300 °C, it is only for microseconds during printing with an additional cellular heating step of 4–10 °C for 2 μs. The result is mammalian cell viability of approximately 90 % [91]. The advantage of bioprinting is that it has little or no side effects and is more accessible, requiring fewer modifications and maintenance than piezoelectric inkjet printers. In reconstructive medicine, skin is an essential tissue that requires effective replacement strategies. 3D bioprinting of fibroblasts and keratocytes over a matrix has allowed the creation of cellularized 3D skin which when implanted into mice formed multilayer epidermis and collagen from graft keratocytes and fibroblasts, respectively. This tissue-engineered skin has demonstrated that 3D bioprinting is capable of creating an in vivo complex multi-cell-type tissue as skin [92•].

## Biomimetics

During the last decade, the development of 3D bioprinting, bioprosthetics, tissue engineering, as well as new synthetic nanostructures has led to the production of macro- and microscale biocompatible, differentiated, and tissue-integrated biomimetic systems. At present, this technology is limited to the production of small tissue volumes of approximately 150–200 μm thickness due to the need for functional vascular systems capable of $O_2$ diffusion [6]. Although 3D bioprinting is a promising technique to fabricate functional vascular systems, to our knowledge no complex arrangements consisting of multiple cell types with the required nutrients and growth factors have been created.

3D-printed organs and engineered tissues ready for implantation present a major challenge for the near future of applied medicine [91, 93•]. Among these challenges is the further development of 3D printing to nanoscale resolution in order to fabricate nanoscaffolds, to fashion new tissue-specific biomaterials, and incorporate virtual reality modeling, 3D imaging, and 3D image reconstruction. Such advancements will ultimately lead to the development of patient-specific implants that will not only have the adequate form, but also the same mechanical, chemical, and physiological properties as original tissues. The bioengineered tissues of tomorrow will ultimately prove capable of cellular differentiation and growth, proving to be tremendously effective means of repair and reconstruction.

## Conclusion

Although 3D printing in plastic and reconstructive surgery is still in its relative infancy, the technology has already proven an invaluable resource. From didactic and training opportunities to constructing educational guides, instruments, scaffolds, or complex organs, 3D printing has opened the door to a heightened degree of individualized patient care. With continued progress in the field of tissue engineering, increasingly complex cell lineages and ultimately tissue types will be designed for implantation at the clinical level. These tissue types will continue to utilize biologic and synthetic materials to supplement and ultimately replace the prostheses of today. With the rapid

maturation of 3D printing facilitating the creation of bioprosthetics, it is within the realm of possibilities to imagine tremendous improvements in quality of life for chronic wound care, amputation, organ transplant, and oncology patient populations or more broadly any patient in need of surgical intervention.

Ultimately, this technology hints at a future free of host–graft incompatibility and an end to graft rejection. With prosthetics composed of cell lineages derived from individual recipients, clinical outcomes will continue to improve, reducing life-threatening postoperative courses and improving cosmetic outcomes. Taken to its logical conclusion, bioprosthetics can conceivably reduce the duration of postoperative hospital stays and perhaps even positively impact the financial burden incurred through implantable device rejection.

As these mechanisms are further developed and made more cost effective, we expect to see 3D printing becoming an indispensable component of reconstructive surgical practice. The theoretical applications for 3D-generated bioprosthetics are all but limitless and offer the potential for an entirely new discipline of medicine; one where the auspices of reconstruction, wound care, immunology, transplantation, engineering, digital design, and material science are intertwined to help treat patients as never before possible.

#### Compliance with Ethics Guidelines

**Conflicts of Interest** Drs. Tepper and Colasante have a patent pending (Number 62/233,543). Dr. Tepper also reports personal fees from Stryker CMF and is a consultant and equity holder for mirrorme3d. Dr. Garfein reports personal fees from Lifecell, Stryker, and Novadaq and is a founder of OscarSurgical. Dr. Sanford declares no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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