

**Review:**

Rapid prototyping technology and its application in bone tissue engineering*

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Received Mar. 16, 2016; Revision accepted July 10, 2016; Crosschecked Mar. 17, 2017

Abstract: Bone defects arising from a variety of reasons cannot be treated effectively without bone tissue reconstruction. Autografts and allografts have been used in clinical application for some time, but they have disadvantages. With the inherent drawback in the precision and reproducibility of conventional scaffold fabrication techniques, the results of bone surgery may not be ideal. This is despite the introduction of bone tissue engineering which provides a powerful approach for bone repair. Rapid prototyping technologies have emerged as an alternative and have been widely used in bone tissue engineering, enhancing bone tissue regeneration in terms of mechanical strength, pore geometry, and bioactive factors, and overcoming some of the disadvantages of conventional technologies. This review focuses on the basic principles and characteristics of various fabrication technologies, such as stereolithography, selective laser sintering, and fused deposition modeling, and reviews the application of rapid prototyping techniques to scaffolds for bone tissue engineering. In the near future, the use of scaffolds for bone tissue engineering prepared by rapid prototyping technology might be an effective therapeutic strategy for bone defects.

Key words: Rapid prototyping; Bone tissue engineering; Scaffolds
<http://dx.doi.org/10.1631/jzus.B1600118>

CLC number: Q819

1 Introduction

The use of biological materials to repair injured tissue dates back to prehistory (Ratner *et al.*, 2004). Now, tissue transplantation (Hernigou, 2014), which was pioneered by Scottish surgeon Dr. John Hunter, has gradually become a reality and has played a critical role in every field of medicine, especially orthopedics. The prevalence of bone disorders caused by trauma, deformity, degeneration, or tumors, and which require bone tissue reconstruction, is increasing yearly. The morbidity of bone fractures and tumors as well as the expenditure on bone grafts continues to rise in both Asia and Western countries (Mithal *et al.*,

2009; Orthoworld, 2011; 2014). These factors constantly promote innovation of the materials and manufacturing processes of bone graft substitutes.

For bone tissue reconstruction, appropriate materials are imperative. As the gold standard for bone defect repair, autografts possess ideal osteogenic, osteoinductive, and osteoconductive properties. However, limited resources as well as donor site infection and pain may limit its development (Campana *et al.*, 2014; Oryan *et al.*, 2014). Although the osteogenic capacities of allografts and xenografts are acceptable, they have risks including potential disease transmission and immunological rejection (Giannoudis *et al.*, 2011; Oryan *et al.*, 2014; Polo-Corrales *et al.*, 2014). Currently, researchers are focusing more on artificial bone substitutes.

Ideal bone graft substitutes should closely mimic the environment of natural bone. The introduction of tissue engineering provides a new approach to repair

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bone defects. The three components of bone tissue engineering, scaffolds, seeding cells, and bioactive factors, form an interactive network. Among them, scaffolds play an important role. Ideal scaffolds for bone tissue engineering should meet the following requirements (Lee *et al.*, 2010; Calori *et al.*, 2011; Bose *et al.*, 2012; Saiz *et al.*, 2013; Narayan, 2014; Polo-Corrales *et al.*, 2014). (1) Inner spaces should possess interconnecting pores, including both macropores (pore size: >100 μm) and micropores (pore size: <20 μm), which are beneficial for tissue growth, substance transplantation, and vascularization. (2) Scaffolds should consist of biodegradable or bioabsorbable materials with strong mechanical properties and controllable degradation kinetics, and should be able to transfer the load to the surrounding tissue. (3) They should have good interface affinity that allows cells to adhere, proliferate, and differentiate efficiently. (4) Scaffolds should be easily prepared at various sizes and shapes. (5) They should regulate the release of biologically active factors. Conventional scaffold fabrication technologies, including solvent-casting/particulate leaching (Huang *et al.*, 2007; Chuenjitkuntaworn *et al.*, 2010; Thadavirul *et al.*, 2014), gas foaming (Montjovent *et al.*, 2005; 2007), phase separation (Ma *et al.*, 2001), emulsion freeze drying (Sultana and Wang, 2008; 2012), and freeze drying (Tabata, 2009), have been widely employed in the biomedical area for several decades. Although they can partially meet the requirements of ideal scaffolds, they still have inherent limitations. Specifically, they are unable to control size, geometry, or spatial distribution of pores, and a random porous structure with low reproducibility does not support bone formation (Hutmacher, 2001). Organic solvents used in fabrication processes pose the risks of toxicity and carcinogenicity to cells (Lee *et al.*, 2010). The ingrowth of tissues is not sufficient because the cells colonize at the scaffold periphery, which will act as a barrier to diffusion of oxygen and nutrients (Sachlos and Czernuszka, 2003). This phenomenon is more apparent after mineralization of the tissue on the scaffold surface (Tabata, 2009). In addition, individualized scaffolds for patients cannot be achieved by conventional scaffold fabrication technologies. Encouragingly, with the emergence of the rapid prototyping (RP) technique, it is possible to solve these problems. The biggest advantage of RP technology is

that it can individualize patients' needs to efficiently apply scaffolds during surgery. Furthermore, it is able to precisely control the inner pore structure with high reproducibility (Lee *et al.*, 2013).

2 Search strategy

To make this review focusing on the basic principles and characteristics of various RP technologies and the application of bone tissue engineering, we searched electronic databases (PubMed, Embase, Web of Science, ScienceDirect) using the terms "rapid prototyping", "additive manufacturing", "solid freeform fabrication", "bone tissue engineering", "scaffolds", "stereolithography", "selective laser sintering", "fused deposition modeling", and "three-dimensional printing" to look for papers published in English from 1995 to 2016 that reported the application of RP technologies to bone tissue engineering.

3 Rapid prototyping technique

RP, also referred to as additive manufacturing and solid freeform fabrication, is a kind of material processing method. Assisted by imaging data and computer-aided design (CAD) models, the RP technique directly manufactures highly accurate three-dimensional (3D) physical entities layer by layer (Frame and Huntley, 2012; Narayan, 2014). Moreover, the RP technique has quickly gained popularity in bone tissue engineering for its high precision, reproducibility, and controllable pore structure (Kim *et al.*, 2012). According to the Wohler's Report 2015 (Wohlers Associates, Inc., 2015), the global market for 3D printing has reached 4.1 billion dollars with a compound annual growth rate of 35.2%. Most notably, medical application is one of the fastest growing areas. The term "3D printing", which is the one most exposed to the public, refers to the RP technique.

A wide variety of technologies are used in RP, which are similar in terms of the main procedures, including the creation and slicing of a virtual computer model followed by the layer-by-layer fabrication process. This process usually involves five steps (Narayan, 2014). First, a CAD model is created or captured from a physical entity by a digital method.

Second, the CAD model is converted into an STL file for virtual slicing. Third, the STL file is sliced digitally into cross-sectional layers, also known as “pre-processing”. Fourth, the RP apparatus creates one layer of the prototype at a time, and then the workstation raises or lowers to the next layer and continues printing until the entire process is complete. Finally, “post-processing”, such as hardening and surface treatment, can be applied depending on the manufacturing technique and purpose.

3.1 Stereolithography

Stereolithography (SLA) is regarded as the first commercial RP technique and can be divided into two main types: bottom-up and top-down (Melchels *et al.*, 2010). The basic principles of this technology are as follows (Figs. 1 and 2). With an aqueous photocurable polymer as the main raw material, SLA uses an ultraviolet laser beam to irradiate predetermined sites

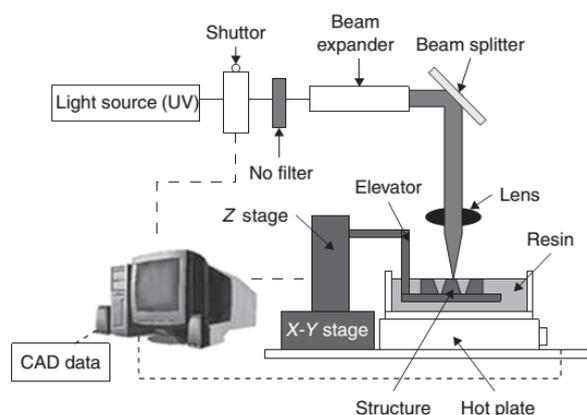


Fig. 1 Schematic diagram of SLA (Lee *et al.*, 2010)

on the material surface, followed by solidification of these areas for photopolymerization, while the uncured peripheral region remains liquid. After solidifying one layer, the lifting table moves to the next layer, and the built layer is recoated with new liquid resin. By repeating this process, the final 3D entity is fabricated layer by layer. Then, the excess resin is drained and washed off.

The key advantage of SLA is extremely high feature resolution. Owing to the emergence of microstereolithography (MSTL), its precision can reach 20 μm (Melchels *et al.*, 2010), which enables SLA to create more complex structures as scaffolds. Lee *et al.* (2011) reported the fabrication of highly porous, fully interconnected scaffolds (Fig. 3) for bone tissue engineering with the MSTL technique and a mixture of polypropylene fumarate (PPF) and bone morphogenetic protein (BMP)-2-loaded polylactide-*co*-glycolide (PLGA) microspheres. In vitro studies showed gradual release of growth factors and excellent differentiation of MC3T3-E1 pre-osteoblasts. Owen *et al.* (2016) used MSTL combined with emulsion templating to produce polymerized high internal phase emulsion (PolyHIPE) scaffolds consisting of two acrylate monomers and isobornyl acrylate. The scaffolds supported osteogenic differentiation of cells. MSTL allowed the individual fibers to be thin enough for cell ingrowth and plasma penetration.

However, the main disadvantage of SLA is the scarcity of available biocompatible resin for the SLA process. The materials used in SLA are mainly based on PPF, trimethylene carbonate, or gelatin (Lee *et al.*, 2010). With continuous exploration and development, researchers are increasing the types of photocurable

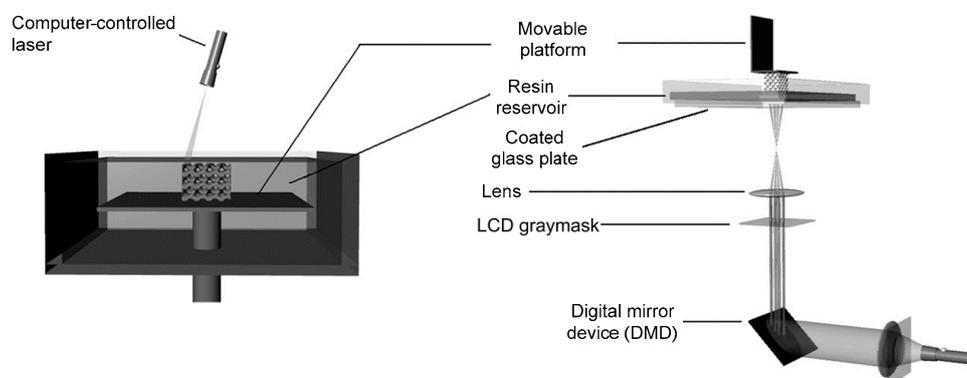


Fig. 2 Schematic diagram of two types of SLA

Left: bottom-up approach. Right: top-down approach. Reprinted from Melchels *et al.* (2010), Copyright 2010, with permission from Elsevier

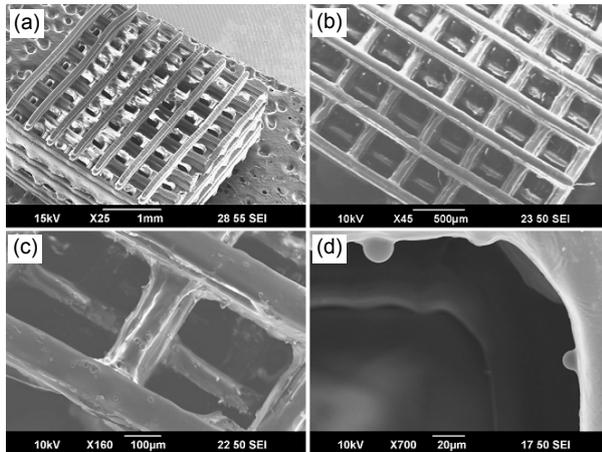


Fig. 3 SEM image of high-precision 3D PPF-PLGA scaffold (a–c) BMP-2-loaded 3D scaffold; (d) Microspheres embedded in the scaffold. Reprinted from Lee *et al.* (2011), Copyright 2011, with permission from Elsevier

polymers and attempting to apply multiple materials (Arcaute *et al.*, 2010). In addition, encapsulation of cells during the process has proved feasible (Chan *et al.*, 2010; Lin *et al.*, 2013). Although this method has not been used in bone tissue engineering, there is a great potential to use this technology in the future.

Given the weak mechanical strength of photopolymerization, researchers have tried to mix certain minerals with raw materials. Ronca *et al.* (2012) fabricated a composite scaffold using a mixture of poly-DL-lactide and nano-hydroxyapatite (nanoHA) with SLA. The presence of HA conferred higher structural strength and better biocompatibility.

Taking another perspective, researchers consider SLA as an indirect fabrication method. Brie *et al.* (2013) used SLA to directly fabricate an HA-resin structure from image data with a mixture of HA powder and a photosensitive resin, and then removed the resin by heating to obtain the final 3D porous HA scaffold. Furthermore, they implanted the scaffolds into bone defect sites of the skull of eight patients. During the 12-month follow-up, no major complications were observed, and X-rays showed perfect continuity between the implant and skull. Du *et al.* (2014) employed MSTL as an indirect RP technique to manufacture negative molds with acrylic resin. After impregnation with β -tricalcium phosphate (β -TCP) ceramic slurry and sintering, the scaffold was complete. It possessed not only the correct external shape

but also an ideal internal structure for bone tissue ingrowth, which was confirmed by perfusion culture and in vitro tests.

3.2 Selective laser sintering

Selective laser sintering (SLS) is also a laser-based system, while its materials come in the form of powders. The basic principles of this technology are as follows (Fig. 4). SLS uses a CO₂ laser beam to heat powder particles to glass transition temperature, which is near their melting point, sintering the material to directly form a solid model without entering the melting phase. Along with the workstation moving down layer by layer, new powder is spread on the sintered object with a roller. The process repeats until the 3D part is complete.

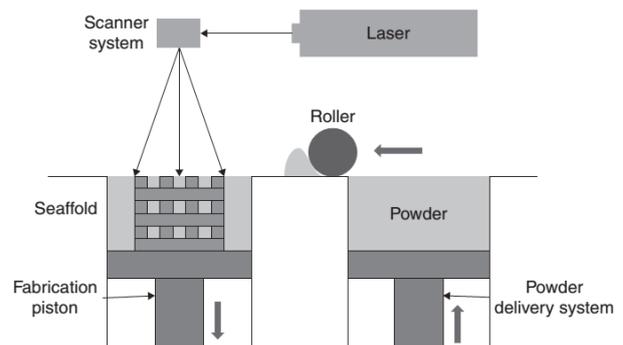


Fig. 4 Schematic diagram of SLS

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Because unbound solid particles support any sintered cantilever structure, SLS does not need temporary support structures, which simplifies post-processing. In addition, material sources for SLS are comparatively wide ranging. For bone tissue engineering, scaffolds can be built through this technique with polycaprolactone (PCL) (Williams *et al.*, 2005), poly-L-lactic acid (PLLA) (Tan *et al.*, 2005), as well as inorganic ceramic (Duan *et al.*, 2010) and their composites (Wiria *et al.*, 2007; Simpson *et al.*, 2008).

The bases of selective laser melting and electron beam melting are similar to those of SLS, except that an intense energy device is used to heat the powder above its melting point, forming a highly dense structure. However, the former two are only suitable for processing a single metal.

The outstanding advantage of SLS lies in its ability to directly fabricate metallic implants that can be applied to repair load-bearing bone. The resolution of features of this technique is determined by the powder size, diameter of the laser beam, and heat transfer in the powder bed (Chia and Wu, 2015). Heat conduction during the process may cause undesirable fusion of peripheral powder particles, which is called the “growth effect”, limiting the resolution of the final construct. SLS can also be used to produce polyetheretherketone (PEEK) scaffolds that are widely applied in orthopedic surgery. Roskies *et al.* (2016) used SLS to fabricate customized porous PEEK scaffolds for seeding mesenchymal stem cells (MSCs) to enhance osteodifferentiation.

Recent research concerning SLS for bone tissue engineering has focused on composite biomaterials. For example, studies have demonstrated the potential of polyvinyl alcohol HA (Wiria *et al.*, 2008) or PCL/HA (Eosoly *et al.*, 2010; Ye *et al.*, 2010; Xia *et al.*, 2013) biocomposites to improve hydrophilicity and mechanical strength. Likewise, a mixture of Ca-P/poly(hydroxybutyrate-co-hydroxyvalerate) (Duan and Wang, 2010; Duan *et al.*, 2011) or carbonated HA/PLLA (Zhou *et al.*, 2008; Duan *et al.*, 2011) may enhance the adhesion, proliferation, and differentiation of cells. Feng *et al.* (2014) fabricated highly interconnected porous scaffolds by SLS with β -TCP doping of zinc oxide powder. They found excellent mechanical and biological properties of these scaffolds by evaluating fracture toughness, compressive strength, osteoinduction, and osteoconduction.

3.3 Aerosol jet printing

During aerosol jet printing, liquid ink droplets are replaced by a focused aerosol stream. A composite suspension is atomized into dense aerosol droplets (usually 1–5 μm in diameter) and then transported to the deposition head via a carrier gas (N_2). In the calibration function of sheath gas, a high-speed co-axial aerosol stream is sprayed onto the substrate layer by layer to create the 3D structure.

Materials, including ceramics, metals, and polymers in the form of a solid or nanoparticles, can be used for aerosol jet printing. Liu and Webster (2011) attempted to use this method to fabricate 3D titanium (Ti)/PLGA nanocomposite scaffolds. In vitro cytocompatibility tests demonstrated enhancement of

the permeability of this kind of scaffold. Furthermore, because aerosol jet printing is a low-temperature process, it is a good candidate for biomanufacturing. The low kinetic energy of droplets does not harm cells. However, there is little research on applying aerosol jet printing to bone tissue engineering.

3.4 Fused deposition modeling

Fused deposition modeling (FDM) is the first RP technique based on extruding a molten polymer. It is a mature technology with broad application, low cost, and rapid processes. Thermoplastic materials in the form of a filament are used as feedstock, and a pinch roller or screw feed mechanism is used to push the filament into a liquefier, followed by extruding fused materials onto the x - y - z platform through a computer-controlled nozzle. Because of the relatively low temperature, the fused filaments solidify and deposit layer by layer to complete the 3D model. Precise temperature control is essential for this procedure to achieve the desired accuracy. The architecture of the scaffold is determined by the nozzle diameter, deposition speed, space between filaments in the same layer, layer thickness, and deposition angle. Theoretically, polymer viscosity and nozzle size dominate the resolution of FDM, which can be relatively high provided there is no extrusion clogging (Narayan, 2014).

The process of FDM is simple and flexible. In addition, it does not require an organic solvent. Regardless of the early studies on collagen, ceramics, PLGA (Yen *et al.*, 2009), and PCL (Zein *et al.*, 2002), or the combinations of metals and polymers in recent years, researchers continue to broaden the range of materials for FDM, such as composite materials and nanomaterials. Li *et al.* (2014) made a comparison between a Ti cage and PCL-TCP scaffold prepared by FDM as a spinal fusion cage (Fig. 5). In vivo experiments showed that despite inferior fusion performance of the PCL-TCP scaffold at 6 months, it had a fusion rate similar to the Ti cage at 12 months. Moreover, the PCL-TCP scaffold resulted in better bone ingrowth and distribution. Jensen *et al.* (2014) fabricated a PCL scaffold with a nanoporous structure by the combination of FDM and thermal-induced phase separation. Excellent osteoconduction and osteointegration were found in their study. Xu *et al.* (2014) manufactured PCL-nanoHA and PCL scaffolds by FDM with commercial artificial bones as

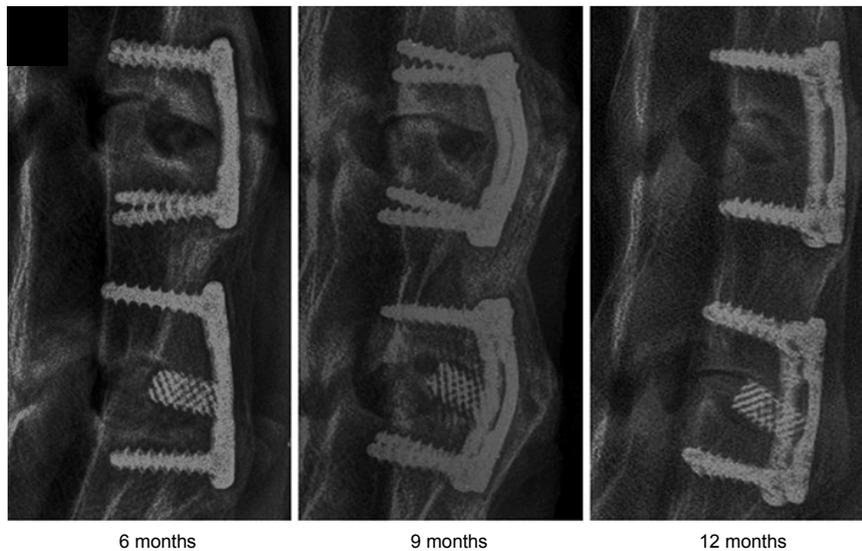


Fig. 5 X-ray examination of harvested specimens at different time points

Top: PCL-TCP scaffold. Bottom: Ti cages. Reprinted from Li *et al.* (2014), Copyright 2014, with permission from Elsevier

the control group. The PCL-nanoHA scaffold was superior in terms of mechanical properties, cell biocompatibility, and in vivo behavior in a long load-bearing goat femur bone segmental defect model. It possessed good biomechanical properties that reduced the stress-shielding effect. Idaszek *et al.* (2015) fabricated a ternary PCL-based scaffold consisting of PCL, TCP, and PLGA through FDM, and its mechanical characteristics, degradation kinetics, and surface properties were evaluated in vitro. As a result, the introduction of PLGA improved the degradation rate and surface roughness.

FDM allows porous scaffolds to form a mesh-like structure that consists of either hollow or solid filaments. Filaments of one layer are usually deposited at a certain angle (0° , 60° , 90° , or 120°) or irregularly, through which a more stable mechanically lay-down pattern is obtained in all directions. To explore the biomechanical properties at various deposition angles, Korpela *et al.* (2013) designed and fabricated PCL/bioactive glass composite scaffolds using five different geometries to test their compressive moduli. Kim *et al.* (2012) also used FDM to fabricate DL-PLGA/ β -TCP scaffolds at deposition angles of 0° and 90° or 0° , 90° , 45° , and -45° . The results showed no significant differences in scaffold degradation or bone regeneration.

The major deficiencies of FDM are the following. (1) Thermoplastic materials narrow the range of

possible materials. (2) The build time of FDM is comparatively long. (3) Heating processes hamper the incorporation of biomolecules into scaffolds. (4) A smooth surface, which is not beneficial for cell adhesion, needs further modification or coating. (5) It is difficult to establish microporosity that promotes neovascularization and cell ingrowth.

To overcome such problems, previous studies (Greulich *et al.*, 1995; Landers and Mülhaupt, 2000; Xiong *et al.*, 2002; Wang *et al.*, 2004; Woodfield *et al.*, 2004; Narayan, 2014) developed a series of nozzle-based RP techniques based on FDM (Fig. 6). 3D fiber deposition, precise extrusion manufacturing (PEM), precision extrusion deposition (PED), and multi-head deposition system (MHDS) tried changing pressure-driven methods (Woodfield *et al.*, 2004), shapes of materials (Wang *et al.*, 2004) and extrusion methods (Kim *et al.*, 2010), and they have been employed to optimize micropore formation. Such methods have improved the efficiency and reproducibility of manufacturing scaffolds with better biocompatibility for bone tissue engineering.

Li *et al.* (2007a; 2007b) evaluated the biocompatible properties of Ti and Ti alloy-biphasic calcium phosphate (BCP) composite scaffolds prepared by 3D fiber deposition. The integration of BCP dramatically enhanced cell adhesiveness and biocompatibility. de Santis *et al.* (2011; 2015a; 2015b) preformed a series of studies and fabricated nanocomposite

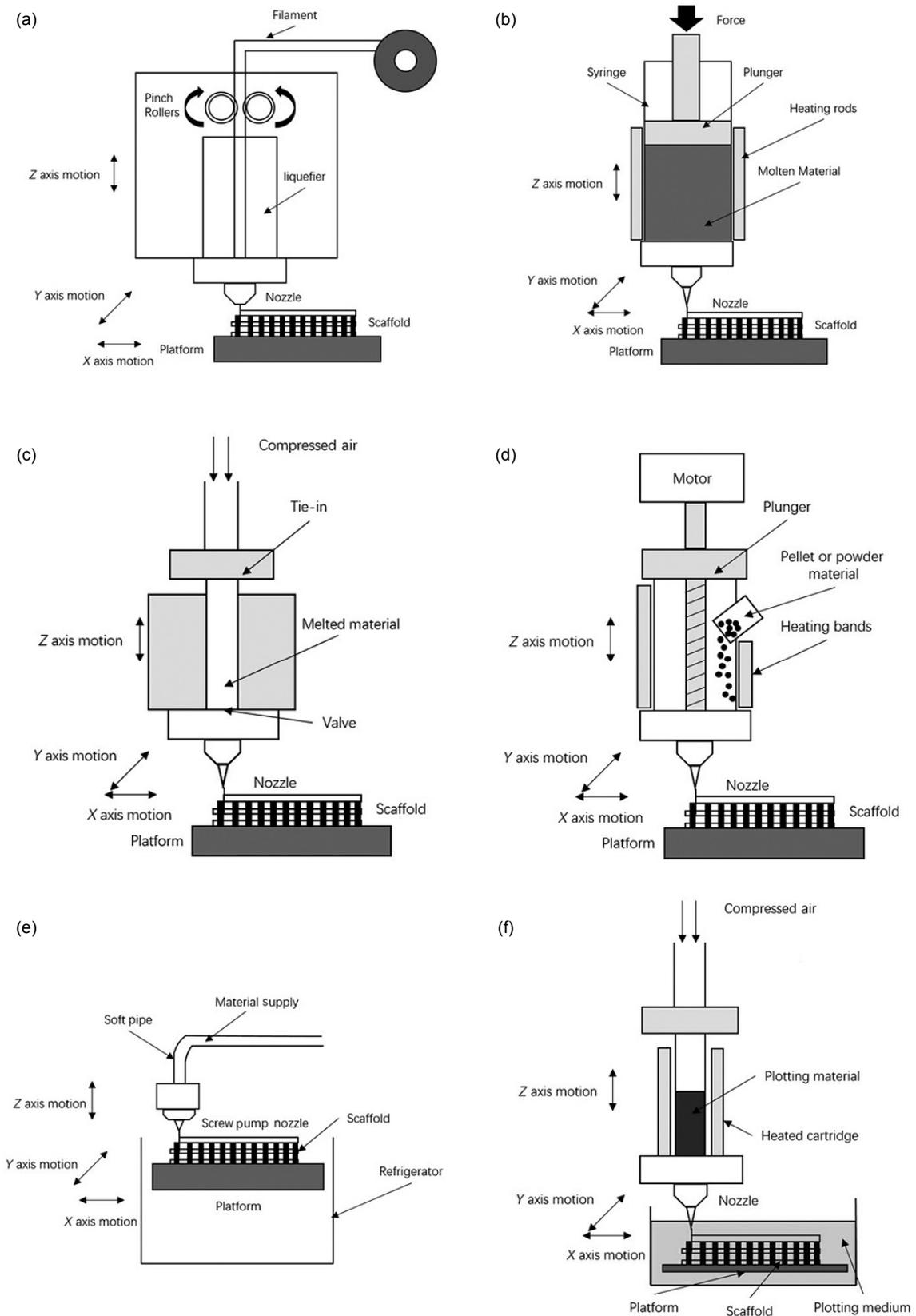


Fig. 6 Schematic diagrams of some nozzle-based systems

(a) FDM; (b) 3D fiber deposition; (c) PEM; (d) PED; (e) LDM; (f) 3D biplotting. The figure is referenced from Narayan (2014)

magnetic PCL scaffolds (the ratio of PCL and Fe_3O_4 was 90:10 (w/w)) and novel PCL/FeHA scaffolds by 3D fiber deposition, which confirmed the feasibility of this technology for bone tissue engineering and the advantages of magnetized scaffolds. Xiong *et al.* (2001) developed a PEM system and fabricated a porous PLLA scaffold using this technique. Morphologies of this scaffold are suitable for vascularization and bone tissue regeneration, and it possesses the appropriate mechanical properties. Shor *et al.* (2007; 2009) used PED to manufacture PCL and PCL-HA scaffolds, and verified the structural integrity, controllable pore size, and good biocompatibility by *in vitro* and *in vivo* studies. Kim and Cho (2009) introduced a novel blended scaffold fabrication technique through MHDS and fabricated PCL-PLGA composite scaffolds. These scaffolds had a fully interconnected structure, porosity of approximately 69.6%, and excellent cytocompatibility with MC3R3-E1 cells. Kim *et al.* (2014) also used MDHS to prepare PCL/PLGA scaffolds combined with a heparin-dopamine conjugate for controlled release of BMP-2 to improve osteoblast activity.

Low-temperature deposition modeling (LDM), robocasting/direct-write assembly, and 3D bioplotting remove the processes of heating and liquefying, and can add thermally sensitive biocomponents or cells into materials.

Xu *et al.* (2010) used LDM technology to fabricate a pearl/PLGA composite scaffold. Scanning electron microscopy, WST-1 assay, and alkaline phosphatase activity assay were used to determine the adhesion, proliferation, and differentiation of MSCs on the scaffold. The new scaffold exhibited better biocompatibility and osteoconductivity than a TCP/PLGA scaffold. Wang *et al.* (2012) also used LDM to manufacture a PLGA/ β -TCP scaffold and coated it with collagen I to enhance bioactivity. Houmard *et al.* (2013) prepared HA/ β -TCP composite scaffolds at various ratios (pure HA/ β -TCP: 60/40 and 20/80 (w/w)) by the robocasting technique. Dorj *et al.* (2013) used this method to manufacture a nano-PCL/HA scaffold, and integrated modified carbon nanotubes into the scaffold to improve mechanical strength. 3D bioplotting has the capacity to prepare scaffolds using the widest range of materials, but its mechanical strength is weak. Schuurman *et al.* (2011) developed a hybrid bioplotting approach to fabricate scaffolds

with a solid biodegradable material and cell-laden hydrogels as its material, resulting in significant improvement of the mechanical properties. Using multiple hydrogels, this method can also build a structure containing multiple cell types and bioactive factors to facilitate cell colonization (Melchels *et al.*, 2012).

3.5 3D printing

3D printing (3DP) has similar principles to SLS without using a CO_2 laser beam. The basic principles of this technology are as follows (Fig. 7). A print head sprays a binder onto a specific location on each layer, and then the strip heater dries the binder. Along with the workstation lowering down layer by layer, a new layer of powder is spread on each layer. The cycle of drop-spread-print-heat is repeated until the structure is complete. Then, extra powder should be removed, and the entire part needs further reinforcement. Packing density, flowability, and wettability of the powder, layer thickness, drop volume, and saturation of the binder may influence the quality of the final product (Bose *et al.*, 2013).

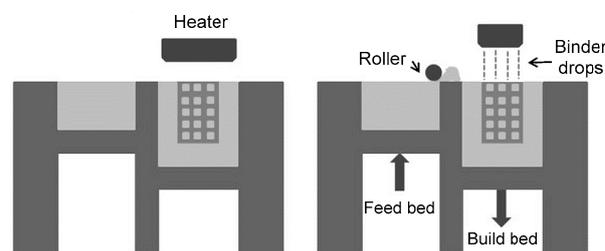


Fig. 7 Schematic diagram of 3DP (Bose *et al.*, 2013)

Unlike the FDM technique, 3DP does not require extra support structures. However, for the porous structures needed in bone tissue engineering, removal of unbound powder is a challenge (Bose *et al.*, 2013). Theoretically, a wide range of biomaterials, including ceramics, metal, polymers, and composite materials can be used for 3DP processes. Furthermore, because the processes are performed at room temperature, heat-sensitive biologically active factors can be added during printing (Chia and Wu, 2015). However, the final products usually have weak biomechanical strength, which require high-temperature sintering to obtain structures suitable for bone tissue engineering (Seitz *et al.*, 2005; Lu *et al.*, 2012; Tarafder *et al.*, 2013; Tarafder and Bose, 2014; Qian *et al.*, 2015).

Exploration of better binders is currently underway (Inzana *et al.*, 2014).

Tarafder and Bose (2014) used 3DP technology to fabricate a TCP scaffold and coated it with alendronate (AD) after sintering. In vivo experiments demonstrated that slow release of AD promoted early healing of bone defects. Qian *et al.* (2015) evaluated the feasibility of scaffolds consisting of Ti and HA prepared by 3DP technology. The pore size was 50–150 μm , and the compressive strength was (184.3 ± 27.1) MPa, which are suitable for bone tissue engineering. 3DP technology has also been applied to indirect methods (Bose *et al.*, 2013; Lee *et al.*, 2013; Chia and Wu, 2015).

4 Conclusions and future directions

Recent years have seen far-reaching improvements in bone regenerative medicine. Along with the development of various biomaterials and manufacturing technologies, researchers have a deeper understanding of bone tissue engineering. RP technologies have overcome some of the shortcomings of conventional scaffold fabrication strategies. Various RP techniques

have distinctive features and advantages, but they all have some deficiencies and problems (Table 1). For SLA, the main challenges are limited material types and poor biomechanical strength of scaffolds. The strategy to overcome these shortcomings is development of new photocurable resins or combining materials. Some new technologies, such as digital light processing (DLP), have promising prospects, although DLP has not yet been used in bone tissue engineering. Both SLS and 3DP result in weak structures. The emphasis of present research is how to improve strength without sacrificing precision. Although accuracy is high, the more precise these structures are, the harder it is to remove the extra powder inside. Therefore, post-processing also needs to be optimized. The applications of nozzle-based RP technologies, such as FDM and 3D bioplotting, are becoming greater because of their rapid development and broad variety.

There remain some difficulties and areas to explore. (1) Although RP technologies can theoretically manufacture subtle regulated scaffolds with uniformly distributed pores, there are few reports on comparisons or research of RP technologies and traditional technologies in terms of osteogenic potential.

Table 1 Comparison of main RP technologies

RP technology	Materials	Advantages	Disadvantages
SLA	PEG, PEGDA, PPF, PCL, PDLLA	Fast speed, high resolution, easy to remove support materials	Limited range of photosensitive resin and polymers
SLS	Polymers, ceramics (PCL, HA, TCP)	Wide range of materials, good mechanical strength, relatively high precision, high porosity	Materials in powder form, difficult to remove trapped materials
FDM	Thermoplastic polymers and their composites	Easy operation, low cost, various lay-down patterns	Materials in filament form, low speed, high temperature, smooth surface
3DF	Thermoplastic polymers and their composites, hydrogels	Easy operation, low cost, materials in pellet form, reduced preparation time	High temperature
PED	PCL, PCL-HA	Materials in pellet form	High temperature
PEM	PLLA, PLLA-TCP	Materials in grain form	High temperature
LDM	PLLA, PLGA, collagen, gelatin, chitosan, alginate	Materials in grain form, retain bioactive agents, can incorporate biomolecules	Need solvent and freeze drying process
Robocasting	Ceramics, organic inks	Wide range of materials, multi-material is possible	Difficult operation
3D bioplotting	TCP, PCL, PLGA, PLLA, soft tissue	Remarkably wide range of materials, biomolecules can be used	Low mechanical strength, smooth surface, slow speed, difficult operation
3DP	Ceramics, polymers, metals	Fast speed, low cost, wide range of materials	Need post-processing, powdery surface

RP: rapid prototyping; SLA: stereolithography; SLS: selective laser sintering; FDM: fused deposition modeling; 3DF: 3D fiber deposition; PED: precision extrusion deposition; PEM: precise extrusion manufacturing; LDM: low-temperature deposition modeling; 3DP: 3D printing; PEG: polyethyleneglycol; PEGDA: poly(ethylene glycol) diacrylate; PPF: polypropylene fumarate; PCL: polycaprolactone; PDLLA: poly-D,L-lactide; HA: hydroxyapatite; TCP: tricalcium phosphate; PLLA: poly-L-lactide; PLGA: polylactide-co-glycolide

In addition, most research remains at the experimental stage, which needs long testing periods before clinical application. (2) Natural bones are not homogenous structures. The design of scaffolds also requires modification. (3) Biologically active factors can only be incorporated into scaffolds during post-processing because of the harsh processes of most RP technologies. (4) Treatment of mass bone defects is still a challenge in bone tissue reconstruction because of unsatisfactory bone graft substitutes.

For further development, RP-based 3D biochemical printing technology and nanotechnology will be key in overcoming the “development bottleneck”. Ultimately, it is of great significance to choose proper biomaterials, preparation processes, and scaffold design. Bone tissue engineering will encounter challenges in the innovation of materials and techniques, optimization of scaffolds, treatment of interfaces, and incorporation of biologically active factors.

Tissue engineering is an interdisciplinary field with improvements achieved by balanced development of various subjects, which is well illustrated by the symbol of clinical transplantation, the chimera composed of a lion’s head, goat body, and snake tail.

Compliance with ethics guidelines

Bo YUAN, Sheng-yuan ZHOU, and Xiong-sheng CHEN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题目: 快速成型技术及其在骨组织工程中的应用

概要: 骨缺损的修复是临床工作中亟待解决的难题, 寻求完善的骨移植替代物一直是各国学者的研究焦点所在。近年来快速成型技术在骨组织工程领域内的应用逐渐扩大, 个性化定制的优势为骨缺损修复提供了新思路。本文对快速成型技术在骨组织工程中的研究进展进行综述, 概述了不同快速成型技术的原理和特点, 总结其在骨组织工程中的应用现状和发展趋势。

关键词: 快速成型技术; 骨组织工程; 支架