Review

Main applications and recent research progresses of additive manufacturing in dentistry

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Abstract: (1) In recent ten years, with the fast development of digital and engineering manufacturing technology, additive manufacturing has already been more and more widely used in the field of dentistry, from the first personalized surgical guides to the latest personalized restoration crowns and root implants. (2) Especially, the bioprinting of teeth and tissue is of great potential to realize organ regeneration and finally improve the life quality. (3) In this review paper, we firstly presented the workflow of additive manufacturing technology. Then we summarized main applications and recent research progresses of additive manufacturing in dentistry. (4) Lastly, we sketched out some challenges and future directions of additive manufacturing technology in dentistry.

Keywords: additive manufacturing; dentistry; application

1. Introduction

Additive manufacturing (AM) is commonly called three-dimensional (3D) printing technology. There are other more synonyms of AM in the research literature, such as additive fabrication, additive processes, additive techniques, additive layer manufacturing, layer manufacturing, freeform fabrication, rapid manufacturing, direct digital manufacturing, and rapid prototyping (1, 2). The American Society for Testing and Materials (ASTM) has defined AM as "a process of joining materials to make objects from 3D model data, usually layer upon layer, as opposed to subtractive manufacturing methodologies" (2). The International Organization for Standardization (ISO), another globally recognized leader in the arena of international standards, declares that the definition of AM shall be in accordance with ASTM F2792 standard (3, 4). AM technology has been developed for nearly 40 years and has reached a maturity level that can be converted into commercial applications (Figure 1). AM technology is based on the data of a 3D mathematical model and continuous layered printing technologies (5). The main advantages of AM technology are improved manufacturing accuracy, simplified production process, economized on materials and human resources, environmental protection, shortened production time, improved production efficiency, and achieved personalized needs. In the field of dentistry, AM technology has been more and more widely used and researched concerning maxillofacial surgery, denture implantation,

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prosthodontics, and orthodontics, from the production of the personalized surgical guides to the fabrication of maxillofacial alternatives, dental implant, and the manufacture of internal crowns, skeletons for implants and dental restorations, etc. (6-8). The application of AM technology has led to the development of dentistry from traditional pure empirical methods to digitization and precision (9). The widespread use of cone beam CT (CBCT) can rebuild three-dimensional maxillofacial and dental anatomy which significantly improves the quality of diagnosis and treatment (10). Bioprinting using AM which incorporates active ingredients such as cells, matrix and growth factors, has shown amazing development potential in the field of teeth, jawbone and periodontal tissue regeneration.

2. Workflow of AM technology (Figure 2)

2.1. Data collection

The collection of 3D data is an important step in model making. At present, there are four common methods: software design, optical scanning, mechanical scanning and radiological scanning. Models designed using design software do not have to be constrained to the size of real objects, and are convenient for calculation, analysis, modification and editing. Optical scanning commonly applies three-dimensional laser scanning, projection raster measurement, Moiré fringe method or stereo photography, etc. It has a higher scanning rate and better accuracy, but the complex shape will make the scanning a blind spot, and errors will occur in the scanned data. With the increase of the freedom degree of the mechanical probe, the scanning blind area will be reduced. Even though, the scanning rate is low and the cost is high. With the development of computer tomography and nuclear magnetic resonance technology, radiological diagnosis has become less invasive and more accurate. The high-resolution 3D image data can be obtained within seconds, making radiological scanning an ideal method for 3D Data acquisition.

2.2. Data processing

It is generally use a special high-performance computer to process the obtained 3D data into the 3D reconstruction software. The scanned data in terms of DICOM (Digital Imaging and Communications in Medicine) format is imported into the software such as Mimics, Geomagic, ProPlan, and Simplant. These types of software can read the DICOM data, set the threshold of different density organizations, construct the form surface, and rebuild the 3D model. Then, the reconstructed data is saved as the STL (Surface tessellation language) format. This kind of three-dimensional reconstruction graphics are stitched together by approximately triangle "fragments". The quantity of triangle "fragments" is positively related with the model accuracy and graph smoothness. Finally, the STL data can be recognized and processed by the 3D printer.

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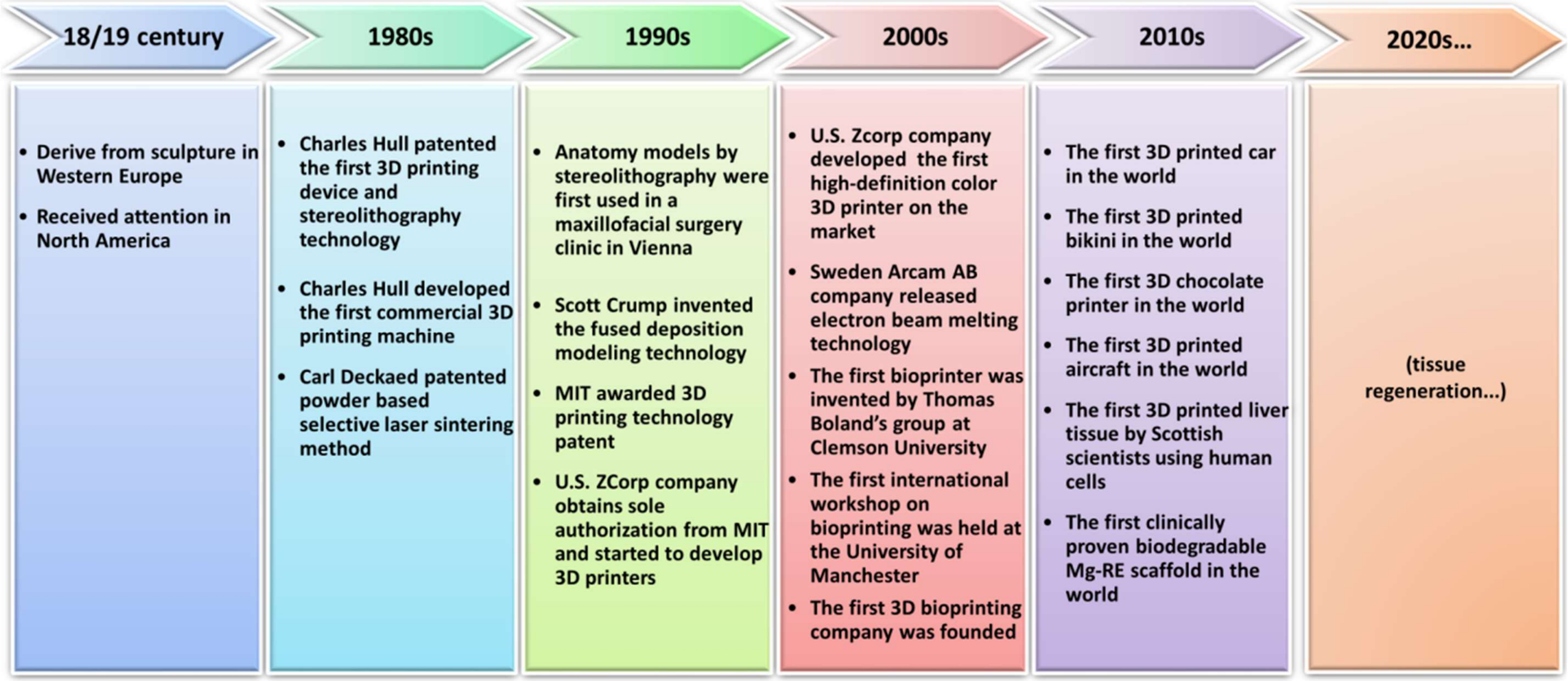

Figure 1. Historical evolution of additive manufacturing

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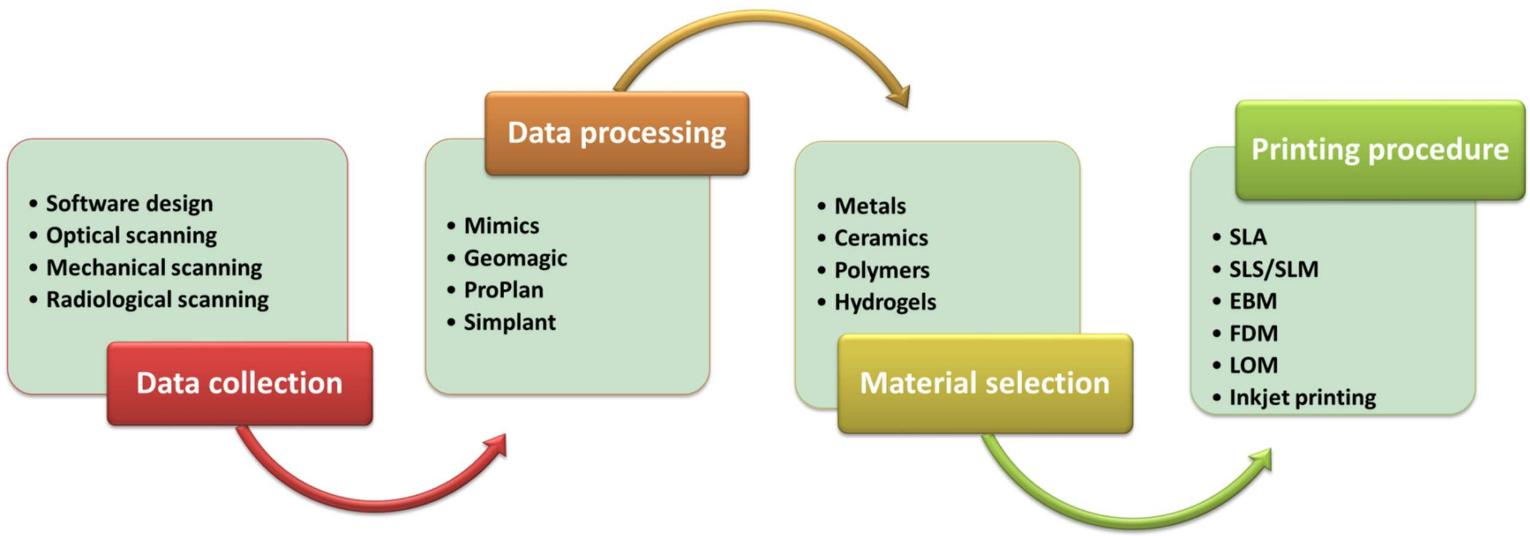

Figure 2. Workflow of additive manufacturing

2.3. Material selection

2.3.1. Metals

In dentistry field, metal products require good mechanical properties, biocompatibility and corrosion resistance properties. The requirements for raw materials are also very strict including high purity, low oxygen content, fine powder size, good plasticity, and good fluidity. At present, 3D-printing metal powder materials mainly used in Dentistry include titanium, titanium alloy, stainless steel, and cobalt chromium alloy.

Titanium and titanium alloy materials have the advantages of small density, high accuracy and large mechanical strength, and good biocompatibility. Porous titanium and titanium alloys have been successfully used in dental application since the end of 1960s (11). Moreover, they are regarded as ideal 3D-printing metal materials (12) and have been widely used, especially in the reconstruction of oral and maxillofacial (13) and manufacturing of dental implant (14). Due to some defects of pure titanium, for example, the strength of pure titanium is not as great as that of titanium alloys, and the elastic modulus of pure titanium is higher than that of bone tissue, which can easily lead to incompatible mechanical stress between titanium implants and bone. Many researchers have tried various ways to improve the performance of pure titanium, such as adding a coating on its surface or oxidized pure titanium surface etc (15-17). Nonstochastic geometries titanium with a periodic repetition of lattice structures shows better mechanical properties and enhanced osseointegration (18). Traini et al. formed a gradient titanium-6 aluminium-4 vanadium (Ti-6Al-4V) titanium alloy porous dental implant, which has more optimized physical and chemical properties. The tensile strength, section shrinkage and elongation are up to AMs4999 (standards on 3D printed titanium alloys issued by ASTM) (19). The elastic modulus of sintered titanium core is similar to that of machined titanium, while the elastic modulus of the porous layer on the surface of this laser sintered titanium alloy implant is reduced thus similar to that of cortical bone. It is beneficial to the long-term stability of the implant (19).

Stainless steels are widely used due to the properties of corrosion resistance, enhanced strength and bargain price (20). 316L (AISI classification) is the most commonly used stainless in the field of maxillofacial reconstruction (21). Cobalt chromium alloys, owing to their wear resistance and high hardness, have been applied successfully for orthodontics and prosthodontics in dentistry (22). The metallic implants can be fabricated using AM technologies which are powder bed fusion processes. Selective laser melting (SLM) and electron beam melting (EBM) are the primarily methods (23).

2.3.2. Ceramics

In dentistry, ceramic materials are required to have aesthetics and biocompatibility as well as low density, high strength, high hardness, high temperature resistance, corrosion resistance, and good physical and chemical properties. Ceramics such as zirconia and alumina are currently used in artificial dental bridges and crowns. Zirconia can be also used in dental implants which display comparable osseointegration with titanium (24). When zirconia ceramics are fabricated by cutting technology, a lot of materials will be cut off resulting in waste and high price of the all-ceramic crown. This craft process may also cause internal

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cracks by cutting forces in the denture. The AM technology in fabricating zirconia ceramic dentures can reach more than 90% of material utilization, lower the price, and reduce environmental pollution (25). Noteworthy, 3D printed zirconia can achieve the bio-imitability such as hardness by printing special internal structures (26). The AM procedure for fabricating zirconia is mainly based on the laser sintering method, but there are some problems such as low density and forming efficiency, and surface cracks (27). Stereolithographic ceramics manufacturing have good surface quality and controllability of structural accuracy (28, 29), and quickly become a research hotspot. At present, there are still some problems in the AM process of zirconia materials, such as large internal stress, cracking after sintering, and volume shrinkage, which may affect its mechanical properties and clinical suitability. Ceramic materials and their fabricating technology still need further investigation.

2.3.3. Polymers

Polymer materials have become the basic mature printing in the field of 3D printing. In dentistry, polylactic acid (PLA), polycaprolactone (PCL), and polyetheretherketone (PEEK) are relatively common 3D printing materials. PLA is an environmentally friendly material with good biodegradability. It can be completely degraded by microorganisms in nature under specific conditions, and eventually generate carbon dioxide and water, which will not cause environmental pollution and is very beneficial to environmental protection Recognized environmentally friendly materials. It also has translucency and gloss texture, making it an ideal material for 3D printing in the field of dentistry. A 3D printed scaffold using a blend of PCL and gelatin has superior mechanical flexibility and softness which could be suitable for soft-tissue engineering such as rhinoplasty. Human adipose-derived stem cell was cultured on this scaffold and showed increased cartilage differentiation and tissue formation (30).

Polyetheretherketone (PEEK) is a thermoplastic polymer. PEEK material has a similar modulus of elasticity to human bones, and the stress of the skull after repair is complete; X-ray transmission performance is good, no metal artifacts are generated, it does not affect medical images, and it is convenient to detect postoperative recovery; Currently, PEEK is used to manufacture denture parts. The Oxford Performance Materials company used PEKK to print craniofacial bone repair patch which has been approved by the US Food and Drug Administration (FDA).

2.3.4. Hydrogels

The hydrogels, typical and commonly used materials in bioprinting, has a 3D network structure with hydrophilic polymer chains, and the water content is 90% to 99%, which contributes to effective oxygen and substance exchange. In the past few decades, hydrogels have achieved unprecedented development in the construction of tissue engineering scaffolds and drug carrier due to their high biocompatibility, low immunogenicity, and adjustable physical and chemical properties (31, 32). The hydrogel multimer system can provide a good matrix for cell transplantation and differentiation, endogenous regeneration, bioremediation, wound healing and continuous drug delivery, while its three-dimensional network system can simulate the microstructure of the original extracellular matrix, Provide living ecological conditions for cell survival (33, 34). However, at present, the hydrogel prepared by 3D

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drawing organisms has low hardness, which may lead to structural collapse or the complexity of shape restriction.

3. Printing procedure (Table 1)

3.1. Stereolithography

Stereolithography (SLA) uses photopolymer to cure by UV laser irradiation. The material of the SLA process is photosensitive polymers which can rapidly polymerize under the irradiation of specific wavelength and intensity ultraviolet light, thereby transfer from liquid to solid with high accuracy. SLA technology has the characteristics of high precision, stable performance and high mechanical strength. Due to the limitation of the material, this printing method needs a supporting structure. The manufactured products are generally brittle and easily broken and require a strict storage (35). This SLA printing technology is widely used in restoration of defected teeth, complete denture base, Resin crown, dowel crown, implant guide and tooth root canal model.

3.2. Laser-based printing

Selective laser sintering (SLS) and selective laser melting (SLM) technology can be vastly used in processing small particles of metal, polymer, and ceramic materials, including titanium and titanium alloy powder, cobalt chrome, stainless steel, nylon powder, elastomers et al. The advantages are high good mechanical property, good accuracy and high material utilization rate. The disadvantages are easy to produce spherification which affects the product quality (36). For metal and metal alloys, SLS is also described as direct laser metal sintering (DLMS) or direct laser metal formation (DLMF) and which is commonly used method in maxillofacial and denture implant.

SLM uses laser to melt metal powder which is a physical-chemical metallurgical change. This technology overcomes the overcomplicated SLS process. The manufactured products have better compactness and higher performance, but are prone to spheroidization which requires continuous improvement and optimization of this procedure (37). SLS and SLM are mainly used in implant guide, implant and alternative of large jawbone defects.

3.3. Electron beam melting

Electron beam melting (EBM) a new type of direct manufacturing technology for metal parts developed in recent years. It is a process of selectively melting metal powders by high-energy electron beams and depositing them layer by layer until the required metal parts are manufactured. EBM technology can easily, quickly and accurately complete the manufacture of extremely complex morphological parts especially can form a complex three-dimensional interconnected pore structure, which provides structural conditions for orthopedic implants to induce bone cell ingrowth Implants have unique advantages and become an important way to meet individual needs (37).

3.4. Fused deposition modeling

Fused deposition modeling (FDM) is to eject molten thermoplastic material such as polycarbonate or eutectic metal powder and immediately solidify it. The material filaments are heated in the hot melt nozzle through the transmission mechanism, then extruded and solidified through the nozzle, and finally formed layer upon layer. The molding speed is fast and relatively accurate, without expensive laser sintering equipment, and the price is relatively low. This kind of materials is mostly used in oral implant prostheses (38). Polylactic acid composite materials (such as hydroxyapatite/polylactic acid, et al.) can be selected to induce the adhesion of osteoblasts in the alveolar socket to the prosthesis (39). Compared with traditional oral prostheses, this technique significantly saves the treatment cost, shortens the operation time and improves the strength of the prosthesis

3.5. Laminated object manufacturing

Laminated object manufacturing (LOM) is to use glue to glue paper or plastic film together, and then use laser to shape. The thin material of LOM adheres layer by layer under the action of hot melt adhesive. The advantage of this technology is that the price of raw materials is relatively low, and the accuracy is acceptable, but the surface of the manufactured product is relatively rough with obvious ladder patterns and easy to crack, so this technology is usually used to make jawbone and denture models, etc. and formulate a comprehensive and effective surgical plan models (40).

3.6. Ink-jet printing

Ink-jet printing (IJP) can be used to print living cells and biological materials to construct a three-dimensional biological scaffold containing different tissues, even living organs. The mixture of hydrogels and cells are distributed into series of droplets using thermally driven nozzle. By layers of printing, three-dimensional structures containing cells can be formed. IJP technology has many advantages such as high resolution, reproducibility, inexpensiveness, and ease of use. Thermally driven IJP is of fast printing speed, and the printing nozzles generate bubbles through local resistance heating, squeezing the liquid in the nozzle to obtain droplets. However, its performance in droplet direction, uniformity and size control is not satisfactory, and the thermal stress, nozzle clogging, cell exposure and other problems generated during the ejection process are often detrimental to printing influences. And the shear force generated by inkjet 3D printing is easy to cause loss of cells. Therefore, improving the survival rate of inkjet 3D printing cells and optimizing the printing process still face challenges (36).

Table 1. Different types of AM technology in dentistry

Technology	company	Energy source	Raw material	Accuracy	Main property	Application
SLA	3D systems (USA) Stratasys (USA) Formlabs (USA) DWS (Italy) Autodesk (USA)	Ultraviolet laser	Photosensitive resin, light curable liquid polymers, ceramic filled resins, etc.	25-35 μm	• High accuracy • Rapid fabrication • Need a support framework • Brittle and easily broken • Strict storage	• Restoration of defected teeth • Complete denture base • Resin, dowel crown • Orthodontic devices (aligners and retainers) • Surgical guide and splints • Tooth root canal model • Maxillofacial model
SLS/SLM (DLMS/DLMF for metals)	3D systems (USA) Blueprinter (Denmark) EOS (Germany)	High power laser	Titanium and titanium alloy powder, cobalt chrome, aluminium, bronze alloy, stainless steel, nylon powder, elastomers ceramics, etc.	20-50 μm	• Good mechanical property • Good accuracy • High material utilization rate • Prone to spherification • High cost • Slow process	• Implant • Alternative of large jawbone defects • Removable partial denture • Metal crown, coping and bridges

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EBM	Arcam (Sweden) FIT Group (Germany) Sciaky (USA)	Electron	Titanium and titanium alloy powder, cobalt base alloy powder, etc.	40-50 μm	• Good accuracy • Rapid fabrication • High energy utilization rate • High power density • Convenient focusing • High cost • Explosive risk	• Implant • Fixation plate
FDM	Stratasys (USA) MarkerBot (USA) RepRap (Germany) Qidi (China)	Extrusion	Thermoplastic filamentous material such as polylactic acid, polycarbonate, PEEK, etc.	35-40μm	• Low-to mid-range cost • Relative accuracy • Fast molding • Good biocompatibility. • Need a support	• Oral implant prosthesis • Edentulous mandible • Surgical guide • Models • Simple anatomical parts
LOM	3D systems (USA)	Laser	Thin material of metal and plastic, etc.	60-70μm	• Rapid fabrication • Low cost • Acceptable accuracy • Low material utilization rate • Rough surface • Easy to crack	• Jawbone model • Denture models • Surgical plan models

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IJP	3D systems (USA) Stratasys (USA)	Electric heater	Powder, Living cells, biological materials, etc.	35-40μm	• High print speed • Low cost • Nozzle plugging	• Teeth • Periodontal tissue • Facial prosthesis

Notes: SLA, stereolithography; SLS, selective laser sintering; SLM, selective laser melting; DLMS, direct laser metal sintering; DLMF, direct laser metal formation; EBM, electron beam melting; FDM, fused deposition modeling; LOM, Laminated object manufacturing; IJP, Ink-jet printing; PEEK, polyether ether ketone. DWS, Digital Wax systems; EOS, Electro Optical Systems; FIT group, Fruth Innovative Technologien group; RepRap, replicating rapid prototype.

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4. Applications and recent research progresses of AM technology in dentistry

AM technology is widely used in the biomedical field due to its high precision and personalized characteristics (41). FDA has cleared some 3D-printed devices for clinical use including orthopedics devices, surgical guides and dental bridges (42, 43). In dentistry, the main applications and research directions of 3D printing in dentistry include: three-dimensional stereoscopic image software combined with prototype models for anatomy teaching guidance, preoperative planning and drills, prognosis analysis and judgment, etc. ; personalized treatment equipment, assistive devices and implants including personalized orthodontic brackets and accessories, restorations, trays, implants and surgical guides; bioactive materials combine living cells and growth factors to print tissues and organs with bioactive functions. However, the bioprinting is still at the stage of printing biological scaffolds due to the complex tissue structure and function (Figure. 3).

4.1. AM Technology in maxillofacial surgery (Table 2)

4.1.1. Reconstruction

Maxillofacial trauma and tumors can cause maxillofacial fractures and bone defects, restore the normal anatomy of the maxillofacial region and language function, which is of great significance to improve the quality of life. In the 1990s, scholars began to try to apply 3D printing technology to the preoperative evaluation of maxillofacial surgery, formulating surgical plans and simulations. Compared with traditional milling models, the stereolithographic 3D models have much higher accuracy (44). And the application of stereolithographic technology has improved the diagnostic accuracy by 29.60% and the operation accuracy by 36.23%, and shortened the operation time by 17.63% (45). In 2012, the Institute of Biomedical Research at Hasselt University in Belgium used 3D printing technology to make a pair of titanium alloy mandibles for an 83-year-old patient. The patient recovered language and swallowing function one day after surgery. Melville et al. and Takano et al. used the CAD/CAM technology to create a model for fibular flap transplantation for partial maxilla resection, and used the model to create a device for guiding the position of the mandible excision and a titanium plate for fibular flap fixation. This procedure shortened surgery time and improved safety, function and esthetic outcomes (46, 47). Haider et al. demonstrated a feasible in-house virtual surgical plan (VSP) and 3D-printed cutting guides in maxillofacial reconstruction. 19 patients with maxillofacial tumors undergoing microvascular bony reconstruction were managed by this technique. The average time for VSP and fabrication of cutting guides was 158 minutes. The average cost was $18.01 Canadian Dollars (48). This in-house VSP and 3D printing is operable for surgeon and benefit for patients.

4.1.2. Orthognathic

Orthognathic surgery is commonly applied to treat skeletal malocclusion which severely affects the occlusion function and the facial features of patients. In the 21st century, AM technology is more and more widely used in orthognathic surgery measurement (49). There are many kinds of 3D printed surgical guiding templates such as repositioning guides, osteotomy and pre-drilling guides.

Dumrongwongsiri et al. used the 3D printed Le Fort I spacers to guide maxilla-mandibular repositioning for 12 patients with facial asymmetry and malocclusion. The average time for preoperative simulation, design and printing of these spacers was 2.5 hours. The average cost was 40 dollars per space. All the patients were satisfied with postoperative facial symmetry and occlusion (50). Wang el al. applied 3D printed mandible model and surgical templates to simultaneously perform orthognathic and mandibular contour osteoplastic for treating mandibular protrusion (51). Shaheen et al. and Heufelder et al. proposed an optimized protocol using 3D planning-printing for bimaxillary orthognathic surgery. 95% of 3D printed splints were clinically accepted (52). The median deviation of maxilla position was 0.39mm between preoperative plan and surgical result (53). Li et al. evaluated a customized orthognathic surgical guide for splint-less bimaxillary surgery. The largest root-mean square deviations for maxillary dental arch, mandibular arch, mandibular body and proximal segments were all below 1.1 mm and 2.82°. The median surgical time was 160 minutes. All patients achieved good final occlusion (54). The personalized orthognathic surgical guide system is accurate and effective for the sake of patients and surgeons.

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Table 2. Application of AM technology in maxillofacial surgery

Author	Application	Cases	Scanning	Software	Material	Process	Main Results
Melville et al. (2019)	Surgery guide and fixation plate in maxillary reconstruction	1	MRI; CBCT	ProPlan (Materialise, USA)	Titanium; polyamide	SLS; FDM	• Precisely correspond with the surgical defect; • Ideally restore the maxilla and midface; • Shorten operative time.
Takano et al. (2019)	Maxillary reconstruction	1	CT	Mimics (Materialize, Belgium)	Titanium	3D printing (Stratasys, USA)	• Improve safety; • Shorten surgery time; • Achieve good function and esthetic outcomes.
Abo Sharkh et al. (2020)	Cutting guides and jaw models in maxillofacial reconstruction	19	CT	3DSlicer (NIH, USA), Meshmixer (Autodesk, USA)	Resin	SLA (Formlabs, USA); FDM (QiDi, China)	• The average time for VSP and fabrication of cutting guides was 158 minutes; • The average cost was $ 18.01 Canadian Dollars.
Shaheen et al. (2017)	Occlusal splints in orthognathic surgery	20	CT (Siemens, Germany); Optical scanner (SmartOp-	ProPlan (Materialise, Belgium); 3-matic (Materialise, Belgium)	Biocompatible Material (MED610)	SLA (Objet Connex 350, Stratasys, USA)	• The mean absolute distance error was 0.4 mm.

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			tics, Germany); CBCT (Planmeca, Finland)				
Dumrongwongsiri et al. (2019)	Spacers in orthognathic surgery	12	CBCT	3-Matic (Materialise, Belgium)	Biocompatible material (MED610)	3D printing (Stratasys, USA)	• Mean preoperative visual analogue scale score was improved by 47.82%; • Mean facial surface area discrepancy index was corrected by 3.16%.
Zhang et al. (2020)	Mandibular models and surgical templates in orthognathic surgery and mandibular contour osteoplasty	10	CBCT	Mimics (Materialize, Belgium)	Plastic	3D printing (Objet Eden 250, Israel)	• The right gonial angle was improved from 128.20° to 120.35°; • The left gonial angle was improved from 129.91° to 120.74°.
Shaheen et al. (2018)	Splints in bimaxillary orthognathic surgery	20	CT (Siemens, Germany); CBCT (Planmeca, Finland); Intraoral scan (3Shape,	ProPlan (Materialise, Belgium) 3-Matic (Materialise, Belgium)	Biocompatible material	3D printing (Objet Connex 350, Strarasys, USA)	• 95% of 3D printed splints were clinically accepted.

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			Denmark)				
Heufelder et al. (2017)	Surgical guides and implants in bimaxillary orthognathic surgery	22	CT (Siemens, Germany); optical scan	ProPlan (Materialise, Belgium)	Not mentioned	SLM	• The median deviation of maxilla position was 0.39mm between preoperative plan and surgical result; • The accuracy of left-right, up-down, anterior-posterior positioning was 0.3mm, 0.33mm, and 0.7mm.
Li et al . (2017)	Cutting guides and fixation plates in bimaxillary orthognathic surgery	10	CT (GE Healthcare, USA); Optical scan (SmartOptics AS, Germany)	ProPlan (Materialise, Belgium) Geomagic Studio (Geomagic, USA)	Ti6Al4V; Photosensitive resin	EBM (Arcam AB, Sweden); SLS (3D system, USA)	• Achieve good final occlusion; • The median surgical time was 160 minutes; • Postoperative nerve parenthesis was recovered with 2-3 months.

Note: cases, the number of patients enrolled in the research; MRI, magnetic resonance imaging; CT, computed tomography; CBCT, cone-beam computed tomography; NIH, National institutes of health; VSP, virtual surgical planning; SLS, selective laser sintering; SLM, selective laser melting; SLA, stereolithography; FDM, fused deposition modeling; EBM, electron beam melting.

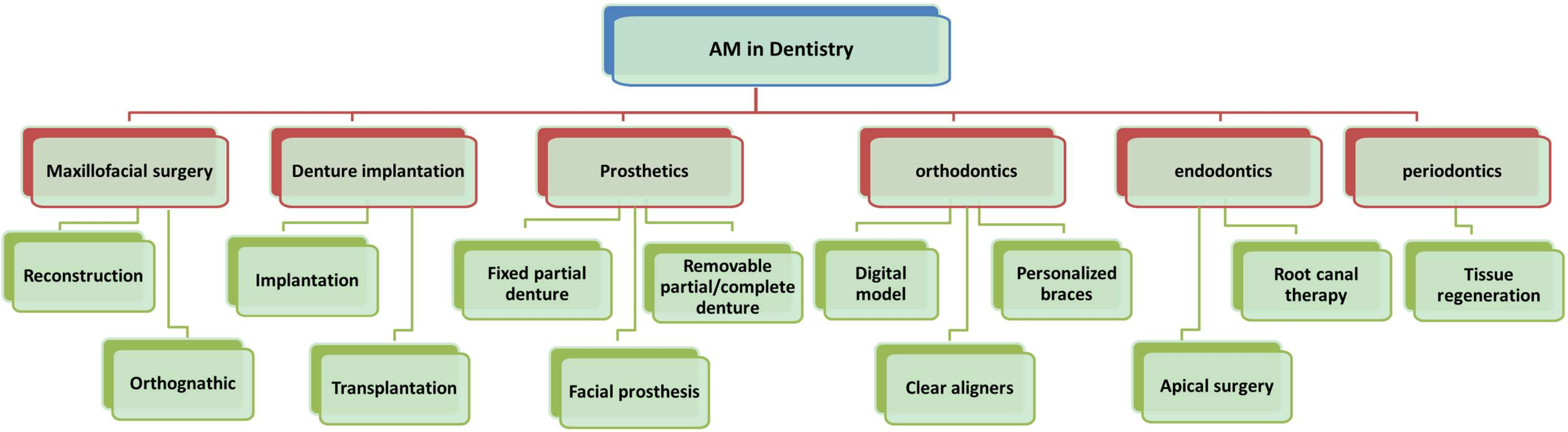

Figure 3. Main applications of additive manufacturing in dentistry

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4.2. AM Technology in denture implantation (Table 3)

4.2.1. Implantation

Denture implantation is a widely accepted and prevail treatment modality to replace lost teeth. AM technology is mainly suitable for patients whose bone mass are inadequate and implants need to avoid important anatomical structures. Compared with commercial NobelActive™ implant, 3D printed porous Ti6Al4V dental implant has higher biomedical parameters and better osseointegration (55). Tunchel et al. launched a multicenter study to check the survival and success rates of AM titanium dental implants after three years' loading. The results with 94.5% survival rate and 94.3$ success rate display a prosperous clinical option for the restore of single-tooth gaps using AM titanium implants (56). Mangano et al. and Figliuzzi et al. successfully placed root-analogue DLMF implants into patients. After 1-year follow up, the implants were of good functional and aesthetic integration (57, 58). Another 4-year follow up research concerning DMLS mini-implants treatment in 62 patients was reported by Mangano research group. The survival rate was 96.9%. The distance between the implant shoulder and the first visible bone-implant contact (DIB) was 0.38mm for 1-year follow up and 0.62mm for 4-year follow up (59).

In addition to the implants, the implant templates are widely process by 3D printing. Mangano et al used 3D printed templates for guiding denture implant in 20 patients with partially edentulous. 96.4% of the templates were steady and suitable for clinical use (60). Recently, Derksen et al. have conducted a prospective cohort study to evaluate the accuracy of 3D printed templates in guiding implant position. Data comparisons were based on CBCT and intraoral scanning. The mean angular deviation was 2.72° and the mean deviations at the implant's entry point and apex were respectively 0.75mm and 1.06mm. Multiple factors such as implant's length and cortical interference may affect the accuracy (61).

4.2.2. Transplantation

Transplantation, in terms of autotransplatation and allogenic tooth transplatantion, is an old technique but is not widespread in dental clinical. With the development of AM technology, this old technique shows a new life. A custom-made implant drill was fabricated by direct metal laser sintering 3D printing system. The allogenic tooth transplantation can be well-fitted in the recipient's alveolar bone using this 3D printed drill. Periapical radiographs showed that the inflammatory and replacement resorption were stable at 4-month follow up after the transplantation. This deemed low-cost modality inspires future researches concerning AM technology for tooth transplantation which reduce bone loss and improve the implant stability (62). In a very recent case report, 3D printed templates were also applied to autotransplantation with good clinical and radiologic results after 2-year follow up (63). Tooth transplantation could be an economic solution for patients by saving costs from an implant, abutment, and crown. In the future, more studies are inspired into this little researched field with the help of AM technology.

Table 3. Application of AM technology in denture implantation

Author	Application	Cases	Specification	Scanning	Software	Material	Process	Main results
Tunchel et al. (2016)	Dental implant	82	Tixos[R] (Leader Implants, Italy) 3.3mm/3.75mm/4.5mm	CBCT	Not mentioned	Ti-6Al-4V alloy	DLMF (Eo-syntM270, Germany)	• 3-year follow up: survival rate (94.5%), success rate (94.3%); • DIB (0.75 for 1 year; 0.89 for 3 years).
Mangano et al. (2014)	Immediate dental implant	15	Root-analogue	CBCT (CS9300, USA)	Mimics (Materialise, Belgium) Magics (Materialise, Belgium) PTC Group (Needham, USA)	Ti-6Al-4V alloy	DLMS (Leader Implants, Italy)	• 1-year follow up: Survival rate (100%); • DIB (0.7mm).
Figliuzzi et al. (2019)	Immediate dental implant in the anterior maxilla	1	Root-analogue	CBCT (CS9300, USA)	Mimics (Materialise, Belgium) Magics (Materialise,	Ti-6Al-4V alloy	DLMS	• 1-year follow up: good functional and aesthetic integration

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					Belgium) PTC group (Needham, USA)			
Mangano et al. (2015)	Immediate loading of four unsplinted implants	62	Tixos[R] (Leader Implants, Italy) 2.7mm/3.2 mm	CBCT (CS9300, USA)	Mimincs (Materialise, Belgium)	Ti-6Al-4V alloy	DLMS (EOSINT M270, Germany)	• 4-year follow up: survival rate (96.9%); • DIB (0.38mm for 1 year; 0.62mm for 4 years); • Biological complications (6%), prosthetic complications (12.9%).
Mangano et al. (2019)	Implant templates	20	Tooth-Supported	CBCT (CS9300, USA)	Nauta (DWS, Vicenza)	Resin	SLA (XFAB2000, DWS, Vicenza)	• 96.4% of the templates were steady and suitable for clinical use.
Derksen et al. (2019)	Implant templates	66	Tooth-supported	CBCT (Morita, Japan)	coDiganosti X (Dentalwings, Canada)	Biomaterial (MED 610)	3D printing (Eden 260V, Stratasys, USA)	• The mean angular deviation was 2.72°; • The mean deviations at the implant's entry point and apex were

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								0.75mm and 1.06mm.
Xu et al. (2019)	Implant drills in allogenic tooth transplatantion	1	Not mentioned	CBCT	Not mentioned	Metal powder	DLMS	• The donor tooth fitted well in the recipient's alveolar bone; • The inflammatory and replacement resorption were stable after 4 months.
Mena-Álvarez et al. (2020)	Autotransplantation templates	1	Tooth-supported	CBCT (White Fox, France)	Not mentioned	Not mentioned	3D printing (Explora 3D lab, Spain)	• 2-year follow up: accurately placement of the donor tooth in the recipient site with good physiological clinical and radiologic results.

Note: cases, the number of patients enrolled in the research; DIB, Distance between the implant shoulder and the first visible bone-implant contact; CBCT, cone-beam computed tomography; Ti-6Al-4V, titanium-6 aluminium-4 vanadium ; SLA, stereolithography; DLMS, direct laser metal sintering; DLMF, direct laser metal formation .

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4.3. AM Technology in prosthodontics

4.3.1. Fixed partial dentures

Due to the complex and delicate anatomical structure in the oral cavity, the denture made by traditional impression methods and traditional restoration techniques is still inadequate. Dental digital impression technology combined with AM technology is expected to improve the accuracy of fixed restorations. AMcan mainly be used to make personalized metal inner crowns, full crowns, and fixed bridges (64). The fitness of the 3D-printed metal inner crown and the prepared tooth is significantly better than the traditional casting metal crown (65). Besides, the application of AM technology in fixed denture greatly simplifies the process, improves precision as well as material utilization. At present, Germany BEGO company has already developed the compact DLP 3D printer to process commercialized permanent single crowns, crown bridges, inlays, onlays and veneers (*https://www.bego.com/3d-printing/*).

4.3.2. Removable partial/complete denture

The traditional removable partial/full denture design and fabrication commonly leads to pressure-induced mucosal pain and residual ridge resorption. Chen et al. combined computer-aided optimization and additive manufacturing to process the jaw model and removable partial dentures. The optimized dentures were evenly attached to the mucosa; the uniformity was improved by 63% and the contact pressure was decreased by 70%, thereby reducing pressure-induced mucosal pain and alveolar bone resorption (66). The computer design system and additive manufacturing technology can also be used to process resin-based completed dentures (67). Due to the maturity of SLM technology, denture titanium alloy stents can be processed to obtain a better fitness for clinical application.

4.3.3. Facial prosthesis

The traditional prosthodontic reconstruction technique is difficult to accurately reproduce the complex defects, thus affecting the repair effect. At present, the AM technology is mainly used in the fabrication of the prosthesis support and the negative mold. The main materials used are metal powder, resin, resin wax, etc. However, the silicone materials for printing are unavailable for a long period. Recently, researchers successfully developed the directly printed silicone prosthesis (68). In addition, Fripp Design Company developed a starch powder-based 3D system for printing medical-grade silicone (69). Unkovskiy et al. applied directly printed silicone prostheses for a 40-year-old woman with a nasal defect. The interim prosthesis was acceptable, however, the position and marginal adaptation before definitive delivery of this prosthesis was difficult to evaluate (70). Even so, this case report hints some cues in directly printed silicone prosthesis. Nuseir et al. compared a direct 3D printing workflow with the conventional workflow for a patient with a nasal defect. The total time required in 3D printed-nose prosthesis was 310 hours, compared with 500 hours in conventional workflow (71). 3D printing workflow can lead to

 doi:10.20944/preprints202105.0685.v1

improved prosthesis reproducibility and aesthetic features and shows a great potential in treatment for patients with facial defects.

4.4. AM Technology in orthodontics

4.4.1. Digital model

The diagnosis and treatment in orthodontics are commonly relying on plaster models. However, plaster models have high requirements on air humidity. If they are kept in places with high humidity, they are easily affected by moisture and deformed. Because of the low material strength, the plaster model is often damaged and loses its reference value in clinical practice. At present, resin models based on intraoral scanning and 3D printing technology have great advantages over plaster models in terms of accuracy, strength and preservation (72).

4.4.2. Personalized brackets

In the beginning of 21 century, German physician Wiechmann first introduced CAD/CAM and SLM technology to produce personalized lingual brackets (73, 74). A recent preliminary clinical trial showed that AMtechnique could also be used to fabricate customized esthetic ceramic brackets whose mechanical parameters were similar to that of commercial ceramic brackets (75). These 3D-printed brackets could better fit the patient's tooth surface with a good aesthetic effect and overcome some drawbacks in traditional orthodontics such as high bracket loss rate, complex indirect redounding, and time-consuming manufacturing process (75).

4.4.3. Clear aligners

The application of clear aligners without brackets is in a rapid development stage; AM technology plays an important role in it. Briefly, the digital model of the dental jaw is reconstructed in three dimensions; then, the computer-aided diagnosis and design is used to simulate the movement of the teeth. After the plan is determined, the simulated dental jaw model is printed out using 3D printing technology; finally, the thermoforming technology is used to make an invisible appliance (76). Currently, 3D printing is mainly used in the production of dentition models. The final invisible braces are still produced via traditional thermoforming technology. The printed appliance cannot be directly used in clinic due to the manufacturing accuracy, strength, and surface characteristics. A recent study showed that 3D printed dental resin-based clear aligners were geometrically more accurate than thermoformed aligners. And the maximum load of 3D printed cured dental aligners was 622N for 2.93-mm displacement. These 3D printed aligners were mechanically stronger than thermoformed aligners (77). This shed light on the whole process of 3D printing in invisible orthodontics. Besides, Cassetta M. had carried out an innovative orthodontic treatment method that combined computer-guided piezocision and clear aligners (78). This combined technique reduced surgical time and patient discomfort, increased periodontal safety and patient acceptability, and achieved accurate control of orthodontic movement without the risk of losing an-

 doi:10.20944/preprints202105.0685.v1

chorage. A 23-year old woman with moderate crowding and a 13-year old male patient with Class II malocclusion have both been treated by this combined method. Treatment duration is greatly reduced to 6-8 months. Oral health-related quality of life and periodontal indexes are both improved after 2-year follow up (79, 80). However, the cases are limited and the follow-up time is not long, we need further investigation and practice to promote the use of this combined technique.

4.5 AM Technology in endodontics (Table 4)

4.5.1. Root canal therapy

The premise of perfect root canal treatment is to establish effective access to dental pulp cavity and root canal system. The 3D printed-templates can be widely used in localization of complex root canals. Fonseca Tavares et al. applied 3D printed templates to access calcified central incisors (81). Maia et al. used 3D printed guides in accessing calcified canals of maxillary premolar and first molar. After 15 or 30-day follow up, all patients were asymptomatic (81, 82). Lera-Mendes et al. applied this 3D printed template to rapidly access the severely obliterated canals of maxillary second and third molars. After 3 months, the periapical tissue was greatly healed by the assessment of radiography (83).

Microguided endodontics is a recent accepted concept in root canal therapy which combines a small diameter bur (0.85 mm) with 3D-printed surgical templates. Conner et al. was the first to use this technique on mandibular incisors (84) and Torres et al. was the first to use this technique on maxillary incisors (85). This novel technique minimizes invasion and apical extended access in incisors with canal calcification and apical periodontitis, whilst shortens operation time on the patients (86). However, microguided endodontics might not be currently used in the posterior region due to the space limitation. There needs further elaborate designs for 3D-printed templates and burs.

4.5.2. Apical surgery

Targeted endodontic microsurgery combined 3D printed surgical guides with trephine burs can enhance the accuracy and efficacy of osteotomy and root-end resection, compared with traditional endodontic microsurgery (87). Antal et al. applied SLA-fabricated surgical templates to resect 3mm apical portion of the root in 11 patients with apical lesions. The mean apex removal and osteotomy depth error were 0.19mm, 0.37mm separately. No recurrence or complications were reported after 6-month follow up (88). Patients who were pathologically diagnosed as periapical cyst or granuloma were treated with precise osteotomy and root-end resection using 3D printed surgical guide. All patients were asymptomatic after 1, 3, or 6-month follow up (89, 90). Popowicz et al. reported the application of 3D printed polylactide surgical guide in 2 cases underwent root-end resection. The two patients were asymptomatic at a 7 or 8-month follow-up visit. Radiographic examination showed complete healing with a radiodense area around the apex of upper left second premolar. The cortical plate at the osteotomy site was restored to the original thickness (91). This targeted endodontic

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microsurgery shows great beneficial in challenging anatomic cases which involve fused molar roots, the palatal root of the maxillary first/second molar, roots of mandibular first/second premolar adjacent to the mental nerve, and roots of mandibular molars with thick buccal bone plate (90, 92). Further studies with a larger group of patients are necessary to obtain landmark conclusions.

Table 4. Application of AM technology in endodontics

Author	Application	Cases	Scanning	software	material	process	Main Results
Fonseca Tavares et al. (2018)	Guided root canal access	2	CBCT	Simplant (Materialise, Belgium)	Not mentioned	3D printing (Objet Eden 260v, Stratasys, USA)	• The calcified root canals of central incisors were successfully accessed; • After15 or 30-day follow up, the two patients were asymptomatic.
Maia et al. (2019)	Guided root canal access	3	CBCT (Icat classic, brazil) Intraoral scanner (3Shape, Denmark)	coDiagnosticX (Dental Wings GmbH, Germany); Simplant (Materialise, Belgium)	Not mentioned	3D printing (Objet Eden260v, Stratasys, USA)	• The calcified root canals were successfully accessed; • After 12 months, the periapical tissue was completely healed.
Lara-Mendes et al. (2018)	Guided root canal access	1	CBCT (iCAT, PA)	Simplant (Materialise, Belgium)	Not mentioned	3D printing (Objet Eden 260v, USA)	• The calcified root canals of tooth27 and 28 were rapidly accessed; • After 3 months, the periapical lesions were reduced.

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Connert et al. (2018)	Miroguided endodontics	1	CBCT (Accuitomo 80, USA)	coDiagnostix™ (Dental Wings Inc., Canada)	Note mentioned	3D printing (Objet Eden260v, Stratasys, USA)	• The obliterated root canal of tooth 31 and 41 was precisely accessed
Torres et al. (2019)	Miroguided endodontics	1	CBCT (New Tom VGi evo, Italy)	3-Matic (Materialise, Belgium)	Biocompatible material (MED 610)	3D printing (Objet Connex 350, Stratasys, USA)	• The obliterated root canal of tooth 22 was precisely accessed; • The apical area was completely healed after 6-month follow up.
Antal et al. (2019)	Root-end resection guide	11	CBCT (iCAT Next Generation, USA)	SMARTGuide (dicomLAB Dental, Hungary)	metal	SLA (ProJet MD 3510, 3D system, USA)	• The median angular deviation was 3.95°; • The mean apex removal and osteotomy depth error were 0.19mm, 0.37mm separately.
Ye et al. (2018)	Periapical surgery guide	1	CBCT (Icat 17-19, USA)	Simplant (Materialise, Belgium)	Not mentioned	3D printing (3510SD, 3D system, USA)	• The root-ends were resected accurately; • The patient was asymptomatic after 6 months.

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Giacomino et al. (2018)	Osteotomy and root-end resection guide	3	CBCT (3-D Accuitomo 170, CA)	Mimics (Materialise, Belgium); Blue Sky Plan (Blue sky Bio, USA)	Not mentioned	3D printing (Objet 260 Connex 3, USA)	• All patients were asymptomatic after 1or 3 months
Popowicz et al. (2019)	Root-end resection guide	2	CBCT (CS8100, Carestream Dental, USA)	DDS-Pro (Natrodent Polska, Poland)	Polylactide	3D printing (Prusa i3 MK2S, Czech)	• The patients were asymptomatic at a 7 or 8-month follow-up visit; • Radiologic assessment showed complete healing with a radiodense area around the apex.
Ahn et al. (2019)	Periapical surgery guide	1	CBCT (Alphrad 3030, Japan)	Ondemand3D (Cybermed, Korea)	Biocompatible clear resin	3D printing (Object Eden260v, Stratasys, USA)	• No postoperative complications were reported

Notes: cases, the number of patients enrolled in the research; CBCT, cone-beam computed tomography; SLA, stereolithography.

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4.5. AM Technology in periodontics (Table 5)

The periodontium is a complex tissue system consisting of several components like cementum, gingiva, and bone. The loss of periodontal tissue caused by periodontal disease is an irreversible process, and its regeneration has been a hot research topic in tissue engineering. The engineering of periodontal ligament (PDL), cementum, and the alveolar bone is based on modular approach. Bioprinting using microfluidic AM technology could manufacture more highly intricate morphologies, internal structures and architectures that accurately replicate the exact anatomical organization and biological function of periodontal tissues (93). A solution containing keratinocytes and fibroblasts as ink components was successfully used to print out the epithelial cell rests of Malassez which is necessary for the initial stage of periodontal tissue formation (93). Periodontal ligament stem cells (PDLSCs) show great potentials in periodontal tissue regeneration under appropriate extracellular matrix (ECM) (94). Gelatin methacrylate (GelMA) and poly (ethylene glycol) (PEG) dimethacrylate composition could serve as ECM materials. Cell and ECM interaction was screened by cell-laden hydrogel array with the help of bio-printing. The cell viability and spreading area were decreased when the PEG ratio was increased (95).

Kim et al. used the compound ink of polycaprolactone (PCL) and hydroxyapatite (HA) as the raw material to align the teeth in vivo and in vitro. The normal anatomical structure of the body was restored, proving the possibility of using dental scaffold to achieve tooth regeneration. Furthermore, cell-derived factor-1 (SDF1) and bone morphogenetic protein-7 (BMP7) on this porous scaffold can recruit endogenous cells with homing effect which facilitate the generation of blood vessel-like, tooth-like and periodontal tissues appear at the interface between the stent and the alveolar bone (96). Park et al. used a 3D bioprinting system to fabricate a PCL scaffold that efficiently promoted alveolar bone regeneration in a beagle defect model (97).

In clinical practice, Rasperini et al. were the first to report a personalized 3D-printed bioresorbable polymer scaffold for a 53-year-old male patient with periodontal defect. After 12-month follow up, the patient gained a 3-mm clinical attachment of periodontal tissue and partial root coverage. However, at the 13-month follow up visit, the scaffold was exposed and larger dehiscence was observed (98). Although this case was unsuccessful in the long term, the approach gave some hints and experience for personalized oral tissue regeneration in clinical settings. Recently, Lei et al applied a 3D-printed periodontal surgery template to guide tissue regeneration in a 36-year-old male patient with severe bone defects of upper right lateral incisor. Advanced platelet-rich fibrin (A-PRF) and Injected platelet-rich fibrin (I-PRF) from patient's blood were mixed with Bio-Oss to form a 3D ideal shape. After a 15-month follow up, the probing pocket depth was significantly reduced to a normal range. And, the alveolar bone was regenerated at the treatment sit by the assessment of radiography (99).

Although, AM has been used extensively in guided tissue regeneration, the microlevel control of scaffold structure is limited by low resolution and material selection. Pilipchuk et al. introduced a novel strategy that combined 3D printing and micropatterning to advance the microlevel design of scaffolds. Results showed that the groove microdepth of scaffold was a more important parameter than width for promoting formation of cell alignment and increasing oriented collagen fiber density. This technique could efficiently achieve the formation of multiple tissues such as alveolar bone, cementum and collagenous PDL-like tissue (100).

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Table 5. Application of AM technology in periodontics

Author	Application	Cases	Scanning	software	material	process	Main Results
Kim et al. (2010)	Guided tissue regeneration (In vivo)	Not applicable	Laser scanning	Not mentioned	PCL, HA	3D printing	• After 9 weeks, a putative periodontal ligament and native alveolar bone were regenerated at the interface incisor scaffold.
Park, et al. (2018)	Scaffold for alveolar bone regeneration (In vivo)	Not applicable	CT	Not mentioned	PCL	3D bioprinting system (laboratory lab-made system in Korea Institute of Machinery and Materials, Korea)	• New bone was formed adjacent to the scaffold; • PCL blocks with 400/1200 lattices were inclined to more new bone formation.
Rasperini et al (2015)	Scaffold for periodontal repair	1	CT	NX 7.5 (Siemens PLM Software, USA) Mimics (Materialise, USA)	PCL	SLS (Formiga P100 System; EOS,, Germany)	• After 12-month follow up, the patient gained a 3-mm clinical attachment and partial root coverage; • After 13-month follow up, the scaffold was exposed.
Lei et al. (2019)	Guided tissue regeneration	1	CBCT	Mimics (Materialise, Belgium)	Biocompatible material (MED 610)	PolyJet (Objet Connex 350, stratasys, USA)	• After 3months, the probing pocket depth was greatly reduced; • After 6 months, bone was regenerated by the assess-

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							ment of radiography.
Pilipchuk et al (2016)	Scaffold for dentin, ligament, and bone regeneration (In vitro & in vivo)	Not applicable	Not mentioned	NX 7.5 (Siemens PLM Software, USA)	PCL, HA	SLS	• Groove microdepth was a more important parameter than width for promoting formation of cell alignment and increasing oriented collagen fiber density.

Notes: CT, computed tomography; CBCT, cone-beam computed tomography; PCL, polycaprolactone; HA, Hydroxyapatite; SLS, Selective laser sintering.

5. Conclusions and Challenges

AM technology is based on a digital model, layered scanning, layer-by-layer stacking forming, and by stacking points, lines, surfaces, and bodies of layer materials, a non-traditional processing technology that quickly produces three-dimensional objects. Compared with traditional technology, AM has some advantages. First, this technology dramatically reduces the duration of treatment. Secondly, the satisfaction degree and comfort level of patients are improved, and the patients can enjoy the convenience brought by personalized treatment and precision medicine. Thirdly, it has greatly improved the working efficiency of clinicians. Currently, it is widely used in maxillofacial surgery, denture implantation, prosthetics, orthodontics, endodontics, and periodontics (101-103).

With the increased clinical demand, it is imperative to transit printing from simple materials to specific biomaterials with physiological activities and functions (104). In the future, AM should be more inclined to tissue regeneration, such as degradable biological scaffolds, reconstruction of tissue and organ structures, permanent replacements in vivo, etc. Despite the advantages of personalization and diversified printing materials, there are still some challenges in the development of AM technology.

(1) The accuracy of 3D printing software, biomechanical properties of raw materials, and resolution of 3D printer are crucial parameters that affect the quality of printed objects in the field of medicine and health care. Therefore, it is urgent to deepen the research on the manufacturing process and optimize the 3D software, materials and equipment.

(2) The microprinter used in dental medicine can really realize in-house/chairside operation. However, the accuracy of 3D printing equipment as well as its intelligence needs to be further improved.

(3) The application of SLM technology to process removable partial denture is mature, but there is still insufficient research on the post-processing technology that greatly impede the large scale application of SLM technology.

(4) In the application of tissue engineering scaffolds, the optimal degradation rate, mechanical properties, porosity and pore size of bone tissue engineering scaffolds are still inconclusive (105). There are few biodegradable materials applied in tissue engineering, and the current 3D printer resolution is in the micron level that hasn't reached the nano level of the jawbone. Therefore, it is necessary to increase the resolution of the 3D printer to improve the scaffold function.

(5) Due to the complex functions of tissues and organs, it may still take a long time to explore the cell sources, and extracellular matrix types, as well as their interaction in the bioprinting (106). Besides, the printing time will affect the cell activity. In order to speed up the printing, the printing pressure or energy intensity is commonly increased, but this will in turn damage the cells inside the stent, thereby resulting in impaired graft function (107). The two facets should be weighed to make a reasonable choice. In addition to technical issues, bioprinting also has safety, ethics, and legal issues. These issues need to be considered during development.

(6) The expensive cost and high application threshold hinder further development of AM. Although the price of 3D printers has been gradually declining in recent years, 3D printers with good quality are still expensive. There also needs high investment in related supporting CT, MRI equipment and computer-aided design software. In addition, the efficient use of equipment and software requires specialized technical training and multi-disciplinary technical personnel division and cooperation.

(7) With the integration of multiple disciplines, AM technology will play a more important role in the diagnosis and treatment of dentistry diseases. Therefore, to establish a thorough and mature collaboration system is urgent.

(8) Emerging concept of 4D printing (3D plus time) (108) that accurately simulate the dynamic transformation of native tissues may remedy the shortcomings of 3D bioprint-

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ing. More researches are required to get new breakthrough in tissue regeneration using AM technology.

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