Orthopedic 3D Printing in Orthopedic Medicine

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Abstract

Orthopaedic surgeries are commonly extremely challenging, and innovations are required to overcome a series of recognised difficulties and improve patient outcomes. Complications, in particular, the high occurrence of infections, often leads to prolonged patient pain, implant failure and loss of functions. 3D printing technology provides an ideal opportunity to integrate cutting edge technologies to address the major identified clinical problems directly. 3D printed orthopaedic implants designed to fit anatomical defects or malformations precisely, can resolve the current limited availability of appropriate well-fitting patient-specific implant parts. Integrated technologies can be included to target postoperative infections, which is an increasingly important concern, particularly considering population demographic and health profile changes. Improved osteointegration technologies can be incorporated to overcome inadequate tissue adherence to implants and bone on-growth. With increasing numbers of patients now outliving their implants, loosening difficulties and premature implant failure rates using conventional technologies are projected to increase dramatically. With these projections, the emergence of 3D printing is a welcome reprieve for patients and surgeons alike. 3D printing technologies hold the promise of significantly advancing current orthopaedic implant capabilities, delivering bespoke customised site-specific implants, which resolve fundamental clinical problems and achieve better results for patients.

This chapter explores the unprecedented solution offered by 3D printed technologies for orthopaedic surgeries. The use of 3D printing for orthopaedic applications and advances, which may lead to future large-scale 3D printed polymeric orthopaedic implant production, is discussed.

Keywords
PEEK, patient-specific implants, 3D printing, surgical jigs

1. Introduction

Orthopaedics is one of the first medical fields to adopt 3D printing technology. 3D printed custom-created artificial bones are currently being utilized as replacements for missing or injured bone. Surgeons around the world are already implanting tens of thousands of 3D printed replacement parts for hips, knees, ankles, sections of the pelvis, spine and skull. 3D printed customised implants can go beyond the realm of where the patient does not fit the standard range of implant size. The inherent geometric freedom of 3D printing is highly advantageous for orthopaedic models and implants as it can fabricate the exact shape and size needed through the anatomical data obtained from medical scanning techniques using a range of suitable materials (Polo-Corrales, L. ; Latorre-Esteves, M. ; Ramirez-Vick, 2013; Thomas and Singh, 2017). Considerable research is ongoing for the development of constructs that support bone formation. 3D printed bone tissue engineering techniques are enabling precise spatial control of tissue scaffold microarchitecture, regulating porosity and pore size, shape and pore interconnectivity to promote osteointegration and bone tissues regeneration (Dehghani and Annabi, 2011; Polo-Corrales, L. ; Latorre-Esteves, M. ; Ramirez-Vick, 2013). Several additive manufacturing techniques have been utilised to fabricate the jigs, scaffolds and implants for orthopaedic applications and this is a promising approach to overcoming the limitations of current treatment options (Bose, S. Tarafder, S. Bandyopadhay, 2016).

The use of 3D printing as patient-specific surgical guides as well as preoperative and intraoperative models from computed tomography (CT) data is already widely implemented (Honigmann *et al.*, 2018). These 3D printed operative models provide surgeons with an enhanced means of physical conceptualisation, which is especially beneficial in complex cases allowing surgeons to pre-select and shape implants (Dehghani and Annabi, 2011; Thomas and Singh, 2017). Furthermore, 3D printing readily enables unprecedented precise tailoring to the subtle nuances of each patient's specific anatomy. 3D printed designs improve the implant fit with the anatomy of the patient, ensuring good bone-to-implant contact and facilitating osteointegration and bony ingrowth (Turnbull *et al.*, 2017). As groundbreaking 3D printing surgeries begin to make the headlines, such as the first ever sternum replacement in the US, the outlook for 3D printed orthopaedic technologies is buoyant.

2. Patient Specific implants

Surgeons need an accurate picture of bone defects to establish the optimal fit for grafts or implants. 3D printed implants meet this need, as they are precisely translated from patient CT and/or magnetic resonance imaging (MRI) data. 3D printed models of specific patient deformities facilitate surgeons in getting to know their patients' anatomy, before entering an operation theatre. The surgeon can study and plan the exact approach and even test procedures, including drilling and bone fixation plate bending, beforehand using a model, which delivers the feeling of the mechanical response of real bone. This technique increases the precision of the 3D detail of a patient's anatomy, compared with conventionally used radiographs, which often provide inadequate information on the extent of bone defects. Recently, there has been a rapid distribution of commercial 3D printers within hospital settings, and 3D printed models are increasingly used in surgical planning for a variety of orthopaedic procedures. 3D printed replica of various fractures and pathologic conditions including spine disorders, dysplasia of hips or bone tumours can be readily 3D printed for surgical planning, allowing the surgeon direct tactile and visual experience which reduces surgical time and associated patients risks due to prolonged anaesthesia.

Accurate, high-resolution image acquisition is the most critical step in making a perfectly representative and well-fitting physical model. The high contrast of bone structure in comparison to the surrounding tissue lends to simple segmentation from standardised Digital Imaging and Communication in Medicine (DICOM) images, in image post-processing. The process of converting DICOM images into a format suitable for 3D printers uses Computed Aided Design (CAD) software, which transforms the 3D images into a series of polygons. This data is translated into Standard Triangulate Language (STL) format, which is appropriate for 3D printers. This format defines individual sections of the 3D image as surfaces that enclose a specific region of space, enabling the 3D printers to add materials layer by layer to fabricate a precise replica model of the 3D image (Giannopoulos *et al.*, 2015; Javaid and Haleem, 2018; Partners *et al.*, 2018). These steps can be listed as:

- A routine CT/MRI scan of the affected area, such as the pelvis, is first performed.
- The axial CT/MRI scan data is reconstructed into thin slices of the order of 0.75 mm at 0.5 mm intervals.
- The DICOM images are extracted for data reconstruction using post-processing software.
- CAD software transforms the images into a series of polygons and converts data into Standard Triangular Language (STL) format, which is compatible with rapid prototyping.
- The STL file is then loaded on a commercial 3D printer.
- Colour may be added to the model by using the ZPR (*.zpr) format.
- 3D printers fabricate 3D physical model by adding material layer by layer. The materials used can be liquid, powder or sheet material, comprising polymers, ceramics or metals.
- The bone-like models are thus printed and air-dried and fixed using different fixatives such as varnish or proprietary solutions.
- Printing time varies from 3 to 6 hours depending on the vertical height of the model.

3. Orthopaedic applications of 3D printing

In the world of bone fixation, a broad range of materials, have been developed to suit the numerous functions of orthopaedic implants. The material selection criteria can vary depending on both the application and the implant type. Here advances in 3D printing of polymers bone orthopaedic applications are discussed based on the medical indication.

3.1. Bone Fixation Devices

The human skeletal system is central to locomotion, respiration, protection of internal organs and supporting body weight. Long bones have additional essential load-bearing functions. There is a variation in the healing time of fractures according to different skeletal sites from 4-6 weeks for the upper limbs to 8-12 weeks for lower limbs, with almost all fractures will take about 3 to 4 months to heal completely. Many of the load-bearing implants utilised to treat fractures of the long bones of the arms and legs are fabricated from metallic materials, due to their high mechanical strength. The annual incidence rate of fractures of long bones is estimated to be 11.5 per 100,000 persons with 40% occurring in the lower limb. The incidence is highest in young men (higher energy fractures) and the elderly (osteoporotic fractures) (Francis D Sheski, 2018). Open fractures of the tibial diaphysis are most common, with open femoral diaphyseal, distal femoral and proximal tibial fractures tend to occur in the most severely injured patients. Lower limb open fractures are more severe than open fractures of the upper limbs (Howe, 2018). 3D printed bone scaffolds hold strong potential for improved non-union outcomes in long bones. 3D printed bone fixation plates which are patient-specific, pre-contoured or pre-bent can contribute to shortened surgery times, reduced patient pain and improved outcomes (Dobbe *et al.*, 2013).

PEEK is an aromatic semi-crystalline thermoplastic polymer with favourable mechanical properties and provides an alternative to conventional metallic or ceramic orthopaedic implants. PEEK has a modulus of elasticity of 3-4 GPa, melting temperature of 334 °C, and glass transition temperature of 145 °C. While the ketone and ether functional groups in the structure of PEEK make it very chemically and thermally stable. PEEK like many other thermoplastic polymers, is hydrophobic which leads to the formation of a fibrous capsule around the implant. This property is advantageous in areas where tissue adhesion is undesirable such as the dura in the skull, muscles around the orbits etc. However, in cases where osteointegration is required to prevent implant loosening and dead spots where bacteria can create biofilms it may be necessary to enhance the bioactivity of the polymer. Many strategies have been tested with particular reference to PEEK as is becoming increasingly popular as a load-bearing implantable material for orthopaedics (Panayotov, I.V. Orti, V. Cuisiner, F. Yachouh, 2016).

The biomechanical properties and bioactivity of PEEK can be improved through surface modification and composite formation (Ma and Tang, 2014). Surface modification approaches include plasma treatment and surface coating as listed in Table 1. Plasma ionised gases can modify PEEK surface chemical and physical properties to deliver enhanced osteointegrative features. PEEK has been treated with oxygen plasma (O_2) (Inagaki *et al.*, 1997), argon plasma (Ar) (Zhang *et al.*, 2011), methane and oxygen (CH_4/O_2) (Awaja *et al.*, 2010), ammonia plasma

(NH_4) (Comyn, J. Mascia, L. Xiao, G. Parker, 1996), oxygen and ammonia (O_2/NH_4) (Waser-Althaus *et al.*, 2014), nitrogen and oxygen plasma (N_2/O_2) (Occhiello, Guerrini and Garbassi, 1992), hydrogen (H_2) (Welle, Weigel and Bulut, 2014), and accelerated neutral atom beam (ANAB) (Khoury *et al.*, 2013). Various bioactive materials have been successfully coated onto the surface of PEEK to improve bioactivity, including hydroxyapatite (HA) (Wu, Hsiao and Kung, 2009), silica (Stawarczyk *et al.*, 2013), titanium (Ti) (Han *et al.*, 2010), gold (Yao, Storey and Webster, 2007), titanium dioxide (TiO_2) (Kizuki and Matsushita, 2015), diamond-like carbon (DLC) (Wang *et al.*, 2010), calcium phosphate (Ha *et al.*, 1997).

Carbon Fibre reinforced Poly Ether Ether Ketone (CFR-PEEK) has being proposed as an alternative to metallic implants. These polymeric implants have the added advantage of enabling bone healing to be monitored in vivo using conventional X-ray without obstruction (Niemeyer *et al.*, 2010). CFR-PEEK have an elastic modulus close to that of cortical bone (18 GPa) and are potential alternatives to titanium, titanium alloys, Cr-Co-Mo alloys and biological ceramics in orthopaedic surgery (Panayotov *et al.*, 2016). IcoTec Medical AG has launched a range of products under the registered trademark Black Amour ®. These implants are based on Carbon Fibre reinforced, and there are several reports of these successful use in orthopaedic applications. PEEK Invibio™ Biomaterial Solutions is the leading manufacturer of medical grade PEEK with a product selection including PEEK (PEEK-OPTIMA Natural), PEEK/HA composite (PEEK-OPTIMA HA Enhanced material), PEEK/short carbon fibre (PEEK-OPTIMA Reinforced) and PEEK/continuous carbon fibre (PEEK-OPTIMA Ultra Reinforced). Other materials and fillers which can be incorporated into PEEK composites, include β-tricalcium-phosphate (β-TCP) (Petrovic *et al.*, 2006), calcium silicate (CS) (Kim *et al.*, 2009), magnesium (Mg) (Jung *et al.*, 2014), nano-silicon dioxide (nano-SiO_2) (Tourani *et al.*, 2013), nano-titanium oxide (TiO_2) (Wu *et al.*, 2012), carbon-nano-fibre (Chan *et al.*, 2016), nano-fluorohydroxyapatite (nano-FHA) (Wang *et al.*, 2014). While many of these implants are manufactured by conventional means, modern 3D printing machines which are capable of handling continuous fibres and polymer filaments such as the MarkFordged ® are capable of 3D printing personalised implants.

While less popular, Glass fibre reinforced PEEK (GFR-PEEK) has also been reported with similar elastic modulus to that of cortical bone (Lin *et al.*, 1997; Wang *et al.*, 2010).

Importantly 3D printing technologies are making progress in the fabrication of PEEK polymer-based implants. 3D printing of PEEK using Fused Filament Fabrication (FFF), can overcome the high melting point challenges and allow construction of almost any complex design geometry. The resulting high precision implants, which cannot be manufactured using other technologies, can offer better fatigue strength, good fracture toughness and radiolucency overcoming the imaging constraints of metallic implants.

Table 1 Approaches to adding osteointegrative properties to PEEK

PEEK Surface modification		PEEK composites
Plasma treatment	oxygen plasma (O_2)	PEEK/carbon fibre
	argon plasma (Ar)	PEEK/glass fibre
	methane and oxygen (CH_4/O_2)	PEEK/ hydroxyapatite (HA)
	ammonia plasma (NH_4)	PEEK/β-tricalcium-phosphate (β-TCP)
	oxygen and ammonia (O_2/NH_4)	PEEK/calcium silicate (CS)
	nitrogen and oxygen plasma (N_2/O_2)	PEEK/magnesium (Mg)
	hydrogen (H_2)	PEEK/nano-silicium dioxide (nano-SiO_2)
	accelerated neutral atom beam (ANAB)	PEEK/nano-HA
Coating	hydroxyapatite (HA)	PEEK/nano-titanium oxide (TiO_2)
	silica	PEEK/carbon-nano-fibre
	titanium (Ti)	PEEK/nano-fluorohydroxyapatite (nano-FHA). Carbon Fibre reinforced PEEK

	gold	
	titanium dioxide (TiO_2)	
	diamond-like carbon (DLC)	
	calcium phosphate	

Postoperative infections are an increasing concern in orthopaedics with infection rates reported between 1-5% for patients receiving devices (Rochford *et al.*, 2016). Additionally, up to 28% of revision surgeries report patient infections. Bacteria readily attach to implant surfaces, proliferating and forming biofilms, inducing inflammation and further medical complications (Veerachamy et al., 2014; Blanchette and Wenke, 2018; Khatoon et al., 2018). Research on the impact of infection on artificial hips and knees, related to 3D printed PEEK implants, has being conducted on developing surface modified 3D printed PEEK with anti-infection properties. Anti-infection 3D printed PEEK orthopaedic implants have the potential to rapidly advance orthopaedic treatments, reduce healthcare costs, and improve patient recovery and outcomes (Webster, 2017).

Traditional methods of mitigating microbial activity on the surface of orthopaedic implants involved incorporation of antibiotics into the bulk implant material as well as fabrication of surface coatings composed of materials with anti-microbial properties. However, considering the prevalence of antibiotic resistance the search for non-coating and non-pharmaceutical means of reducing implant-associated infection is of great importance. One current alternative to traditional methods of making implant surface anti-microbial has been to reinforce the surface of orthopaedic materials such as PEEK with nanosized physical features. Generally, this can be achieved utilizing simple template-moulding methods, in which a material with a unique structure is used as a template to imprint its structure onto another article (Hong, Hwang and Lee, 2009). A study by Kelleher et al. used a nano-topographical pattern closely replicating the naturally hydrophobic and anti-microbial structure of the cicada insect wing which is composed of randomly interspaced nanopillars (Kelleher *et al.*, 2016). Subsequently, the research group compared levels of bacteria culture proliferation on commercial orthopaedic PEEK and the nanosurface modified PEEK. The results showed a 40% and 50% reduction in levels of Staphylococcus epidermidis and Pseudomonas aeruginosa respectively after five days on the nano surface modified PEEK compared to that of the commercial PEEK (Wang, Bhardwaj and Webster, 2017). This is primarily due to the physically destructive effect of the nanopillars on the membrane of bacterium which is generally not seen with mammalian cells due to their larger and more robust nature (Bagherifard *et al.*, 2015). 3D printing can potentially be used to produce nano topography on the surface of medical devices directly. This approach could be advantageous as it would simplify the regularity approval pathway as no active pharmaceuticals are used.

It is also reported that surface wettability and associated surface energy of the implant material can ultimately lead to promising antibacterial properties and desirable cellular functions. Liu *et al.* reported a direct linear correlation between surface energy and surface roughness and that surface energy plays a significant role in determining cell and bacteria functionality (Liu, 2017). Moreover, the incorporation of nano-textured silicon nitride onto the surface of orthopaedic implants are being investigated and has been shown to decrease bacterial growth and encourage the formation of bone simultaneously. It is suggested that silicon nitride is textured in a way that attracts osteoblasts and repels microbes (Ishikawa *et al.*, 2017). Recently, implants comprised entirely of silicon nitride have been fabricated using a new emerging AM technique Robocasting (Koslow, 2016).

Another area of interest in the field of bone fixation is that of fully biodegradable bone-fixation devices which appear to be great alternatives for patients. These implants have several advantages over traditional materials due to their biodegradation once their function is fulfilled. These advantages include no need for implant removal, minimal risk of implant-related complications and early functional rehabilitation. Fully biodegradable bone-fixation devices are often made of biodegradable polymers such as Polylactic acid (PLA), Polyglycolic acid (PGA), PolyLactic-co-Glycolic acid (PLGA), Polydioxanone (PDO), polysulfate and polycarbonate. PLA is a relatively strong biodegradable polymer and has been used intensively in medical applications. With L- and D-enantiomeric forms of lactic acid, PLA appears as PLLA with only the L-isomer, poly(D-lactic acid) (PDLA) with just the D-isomer, poly(D,L-lactic acid) (PDLLA) with half L-isomer and half D-isomer, and PLA with a majority of the L-isomer and a small amount of the D-isomer. These polymers are frequently melt processed by extrusion which is fundamentally the technology used in FFF. As such customisation of implants from these polymers is relatively straight forward.

Biodegradable bone-fixation devices which biodegrade in an osteotransductive manner have many advantages over non-biodegradable counterparts. Loosening of permanent implants is a severe complication requiring subsequent surgical removal of these implants. Removal of permanent implants in the spine due to instability or dislocation may leave a deficit leading to instability of the spine. Therefore, biodegradable fixation devices, offer an ideal option for spine fixation. Indeed, biodegradable bone-fixation devices are superior to traditional metallic devices in terms of biocompatibility and functional recovery. Research has been conducted to compare tissue reactions to titanium and biodegradable screws upon postoperative irradiation in rats. In this study, biodegradable screws induced a lower inflammatory response compared to titanium screws which led the researchers to hypothesise that biodegradable screws may be safer reconstructive devices for patients undergoing radiotherapy. Several studies have shown the rate of infection and plate removal of biodegradable plates to be significantly lower when biodegradable plates are utilised instead of titanium plates.

The benefits of 3D printed biodegradable fixation devices outweigh those of traditional bone-fixation devices. Polymer implants do not interfere with imaging and allow a clear view of fracture sites on radiographs. 3D printing of patient-specific implants eliminates the need to shape the implant during surgery and bending instruments such as pliers, are not needed to place biodegradable plates against bone surfaces (Ellis and Walker, 1996). There is no need for a procedure to remove them, which reduces costs and there is evidence that biodegradable bone-fixation devices promote better bone healing than traditional plates and screws. However, there are drawbacks to the use of 3D printed biodegradable implants which include: the need to pre-drill and tap holes for biodegradable screws which increases the operative time, more difficult implant placement due to concerns with heat generation during drilling and polymer debris has been reported to cause an inflammatory foreign-body reaction.

3.2. Craniomaxillofacial

Craniomaxillofacial (CMF) plastic and reconstructive surgeons specialise in the soft tissue and skeletal structure of the skull and face. The face defines and expresses our identity and individuality and is enabled by the incredibly complex structure of the facial skeleton. Reconstruction of craniomaxillofacial defects and deformities, which arise as a result of congenital defects, cancers and injuries, require consideration of both functional and aesthetic objectives. Reconstruction aims to restore volume, shape, bone continuity and symmetry of the bone skeleton. Oral maxillofacial soft and hard tissues enable functions such as mimics, mastication, swallowing and articulation. Restoration of multifaceted maxillofacial geometry such as orbital wall contours involves mastery of complicated and specific 3D anatomy and can also present significant clinical risks. In the case of orbital reconstruction, the reproduction of the contralateral unaffected orbit may result in clinical failures such as diplopia, enophthalmos and blindness, for even the most experienced surgeons (Chul *et al.*, 2017). Implant fit in this region is critical as ill-fitting implants can be visible under the skin or can cause discomfort or irritation to overlying tissues. Hence, 3D printing of biodegradable implants is highly advantageous in this region. Biodegradable polymers have already been successfully utilised in this field, and it has been reported that maxillofacial fractures which were treated with biodegradable Inion CPS® reported favourable healing and no local tissue immune reaction. Biodegradable fixation devices have adequate shear resistance, but less load resistance and stiffness compared with titanium, which helps to avoid stress shielding and promotes healing. Additionally, as bones of the CMF region are not loaded this is not considered a significant concern with studies showing that fractures of the mandibular body using Inion CPS® showing sufficient mechanical strength and fixation stability. The use of biodegradable fixation devices is a promising technology, and a reasonable degree of healing can be achieved in patients of all ages, as well as mandible fractures in early childhood (Gaba *et al.*, 2014; Ali *et al.*, 2016).

Significant advances in craniofacial reconstruction have resulted from the development of rigid biomaterials and medical modelling based on 3D printing over the last 15 years. Accurate but nonsterile 3D printed models of a patient's maxillofacial skeleton can readily be produced using CT data. Widely used 3D printed prototype models provide: (Mohamed, Beherei and El-Rashidy,

2014) aids for the production of surgical implants, (Wang and Yeung, 2017) surgical planning improvements, (Thomas and Singh, 2017) service as orientation aids during surgery, (Polo-Corrales, L. ; Latorre-Esteves, M. ; Ramirez-Vick, 2013) enhanced diagnostic quality, (Dehghani and Annabi, 2011) assisted preoperative simulation, (Bose, S. Tarafder, S. Bandyopadhay, 2016) achieving a patient's consent prior to surgery, and (Turnbull *et al.*, 2017) resection templates for surgeons, as well as providing an educational tool for medical students (Choi and Kim, 2015).

A facial prosthetic fitting is much quicker than full reconstructive surgery, offering patients a low risk and high impact treatment option to address underlying facial defects. Conventionally facial prosthetics are handmade, require several labour-intensive manufacturing phases and numerous patient consultations. Production is, therefore, a time-consuming, costly and a highly subjective process, being highly dependent on the skills of the anaplastologist (Peart *et al.*, 2017). High-resolution 3D printing has been demonstrated to deliver superior auricular prosthesis's, which provide patients with a realistic look while streamlining the current production methodology. Accurate topology of the patient's uncompromised anatomy from CT scan data is used to print a 3D mirrored template to use in the casting process for prosthesis production or for the direct 3D printing of a prosthetic such as an eye or ear for patients who have lost or were born without them. While currently, 3D printed prosthetics do not restore function, these prosthetics can be seamlessly incorporated into the patient's face providing a highly realistic outcome (Mohammed *et al.*, 2018).

A recent study developed a computer algorithm to create a 3D nose model based on 2D photographs, which is similar in appearance to the patient's actual anatomy (Isaiah, Greywoode and Vakharia, 2018). 3D printed high-impact polystyrene nasal prosthetics were created for five volunteers. Surveyed clinical evaluators indicated that they would consider using this technology to create a temporary prosthesis instead of referring to an anaplastologist. 3D printed patient-specific implants provide a personalised approach to reconstructive and esthetic maxillofacial surgery. Maxillofacial patient-specific implants can now be designed using preoperative imaging data for input into computer-aided design (CAD)/computer-aided manufacturing for fabrication using 3D printing. This approach increases precision and decreases or eliminates the need for intraoperative modification of implants (Owusu and Boahene, 2015). 3D printed patient-specific implants have been successfully used in mandible reconstruction (Rana *et al.*, 2017), cranioplasty (Zegers *et al.*, 2017), and orbital reconstruction (Stoor *et al.*, 2014). Furthermore, customised implants have reduced implant-related complications, improved surgical accuracy, increased surgical speed, improved quality of life, decreased postoperative pain and provide aesthetically good results.

In a study evaluating one hundred and four patients with immediate orbital defect reconstructions and twenty-three post-traumatic orbital deformity reconstructions using mirror-imaged rapid prototype skull models and a pre-moulded synthetic scaffold, all reconstructions were successful without immediate postoperative complications (Park, Choi and Koh, 2015). 3D simulation was performed using Mimics 3D software (Materialise NV, Inc., Leuven, Belgium). The unaffected orbit was reflected onto the contralateral side by mirroring techniques, and then rapid prototype skull models (AMK, Inc., Goyang-si, Gyeonggi-do, Korea) representing the individual model of the uninjured state were generated using a 3D printer (Projet 660 Pro; 3D Systems, Inc., Rock Hill, SC). Synthetic scaffolds were anatomically pre-moulded using the skull model as a guide and inserted into the orbital defect. 3D-printed CMF devices and patient-specific implants are being found to outperform their conventional comparators consistently. The availability of inexpensive compact desktop 3D printers, high-performance biocompatible materials and excellent patient outcomes is now paving the way for surgeons to access on-site production of medically certified 3D printed patient-specific implants in hospital settings.

3.3. 3D printing for the repair of Pelvis Fractures

Ageing populations are now requiring more orthopaedic surgeries, with a doubling in annual joint replacements operations reported in the United States between 2000 and 2010. 3D orthopaedic printing technologies are also advancing at a considerable rate which is benefiting complicated sections of the skeleton such as the pelvis. In 2011, the first 3D printed pelvic implant was carried out on a patient suffering from chondrosarcoma, who required half of his pelvis replaced due to the bone cancer. 3D printed mirrored pelvic implant surgery is a further approach, which has been made available by 3D printing. In this technique, surgery teams use a

3D model of the healthy hemipelvis to pre-contour the plates using the assumption that the healthy hemipelvis was anatomically symmetric to the fractured half (Upex, Jouffroy and Riouallon, 2017). Using DICOM files, OsiriX™ software was used to generate a 3D volumetric reconstruction and surface rendering of the fractured and healthy hemipelvis ready for export as STL files. The healthy hemipelvis was mirrored (reversed horizontally) and 3D printed along with the fractured hemipelvis using a 3D printer (Ultimaker™, Geldermalsen, Netherlands) using polylactic acid (PLA) (0.15 mm layer thickness, 100 mm/s extrusion speed, 20% filling).

The feasibility of 3D printing technology in pelvic endoprostheses and artificial hip joints for patients suffering from pelvic tumours has been demonstrated. Between September 2013 and December 2015, 25 out of 35 patients that underwent complete pelvic reconstruction surgery at the hospital, survived without significant complications. The research team are supporting 3D printing as a viable and practical route for the precise matching of implants and patient host bone (Liang, H., Ji, T., Zhang, Y., Wang, Y., Guo, 2017). Further research also supports the use of 3D-printed pelvic prostheses for reconstruction of the bony defect after pelvic tumour resection, stating its safety, the lack of additional complications, and the good short-term functional results experienced by patients.

The application of 3D printing has been reported for improved surgical outcomes for often devastating both-column acetabular fractures, which are breaks in the socket portion of the ball and hip joint where the fracture plane travels vertically through the innominate bone, dividing it anteriorly and posteriorly into at least three fragments. 3D patient-specific printed models of the pelvis facilitate preoperative planning, simulation of the fracture reduction procedure and pre-contouring of the fixation plates contributing to good medium-term functional outcomes.

3.4. 3D Printing in Bone Tissue Engineering

Conventionally, non-union fractures are treated using autografts, which meets the required properties in terms of osteoconduction, osteoinduction and osteogenesis, as it contains both osteogenic cells and osteoconductive mineralised extracellular matrix material that promotes cell growth and proliferation (Polo-Corrales, L. ; Latorre-Esteves, M. ; Ramirez-Vick, 2013). Nevertheless, autografts are restricted by the size of the graft that can be harvested and carry a risk of donor morbidity including infection and ongoing pain following surgery (Turnbull *et al.*, 2017). The alternative, known as allografts where bone tissue is harvested from cadaveric and living sources are also widely adopted as this approach can eliminate the donor site morbidity. However, allograft drawbacks include the potential risk of disease transmission and immune rejection (Polo-Corrales, L. ; Latorre-Esteves, M. ; Ramirez-Vick, 2013), in addition to also lacking a cellular component to aid tissue regeneration (Turnbull *et al.*, 2017). Orthopaedic fixations using plates and screws as well as bone cement and substitutes are a mainstay approach to aiding bone regeneration. These approaches have considerable limitations including bone thinning due to stress shielding, loosening and failure over time, resulting in the need for revision surgeries. Non-invasive therapies such as ultrasound treatment have shown promise for aiding bone healing by delivering ultrasound waves with low-intensity pulses to accelerate the healing of non-union fractures in suitable adult patient long bones (Higgins, Glover and Yang, 2014).

Porous 3D bone tissue engineering scaffolds are currently the subject of intense research due to their recognised potential for osteoconduction, osteoinduction and osteogenesis. 3D printing scaffolds with spatially controlled scaffold microarchitecture can be fabricated using stereolithography, fused deposition remodelling and selective laser sintering. In new emergent technology 3D, bioprinted scaffolds have been demonstrated through inkjet bioprinting, laser-assisted bioprinting, microvalve bioprinting and extrusion bioprinters (Turnbull *et al.*, 2017). Examples of the use of polymer-based 3D printing in these applications include: incorporating 3D printing, electrospinning and a physical punching process to create a composite polycaprolactone/alginate construct with nanofibrous content and improved mechanical strength (Kim *et al.*, 2009). This method showed a significant enhancement of cell viability within seven days, with evidence of a high increase of osteoblast formation at 14 days and considerably increased water absorption due to the improved hydrophilicity contributed by the scaffold alginate content. Porosity can be added to the composite polymer-ceramic scaffolds using techniques including 3D printing and electrospinning which are capable of depositing material within gaps between fibres thereby facilitating interconnectivity. The scaffold micro and macroporosity can also be modulated by using a combination of porogens with 3D printing techniques during the fabrication process. Cheng et al. describe combining polydopamine (PDA)-coated/HA precipitate in developing polycaprolactone scaffolds using stereolithography technology, fabricating 3D structures through spatially controlling the solidification of liquid photo-polymerisable resin (Cheng, Y.L. Chen, Y.W. Wang, K. Shie, 2013). Injectable hydrogels have also attracted significant attention within bone and cartilage tissue-engineering applications due to its potential advantages in the ability to perform minimally invasive injections and the capacity to mould hydrogels in situ to match irregular patient defects.

3.5. 3D Printed fixtures and jigs for surgical applications

The primary function of customised surgical guides/instruments (CSG/CSI) is to guide, direct and fix locations for the use of surgical tools including drilling, cutting and sawing tools (Figure 1). Hananouchi et al. described CSGs as being made up of two working components: (Mohamed, Beherei and El-Rashidy, 2014) a guide, i.e. cylinders, holes and slots for tool guidance and (Wang and Yeung, 2017) a base part for fixation of the guide directly onto the patient's anatomy (Hananouchi and Saito, 2010). CSGs are a bi-product of virtual surgery planning, a pre-operative technique that emerged out of advancements in medical imaging technologies and image processing software. Virtual surgery planning utilises personalised, highly accurate CAD models of patient anatomy to improve procedure and outcomes of complex surgeries (Oliveira *et al.*, 2008; Azari and Nikzad, 2009; Logan *et al.*, 2013; Shen *et al.*, 2017). CSGs have also been referred to in the literature as patient-specific instruments, surgical jigs, fixtures, blocks, templates and stents (Oliveira *et al.*, 2008; Dahake *et al.*, 2016). Wherein all of the above refer to tools or aids that are specifically designed and manufactured by engineers with input from surgeons using CAD and rapid prototyping technology to improve pre-surgical planning and/or improve operative efficiency which is generally very time sensitive where orthopaedic surgery is concerned.

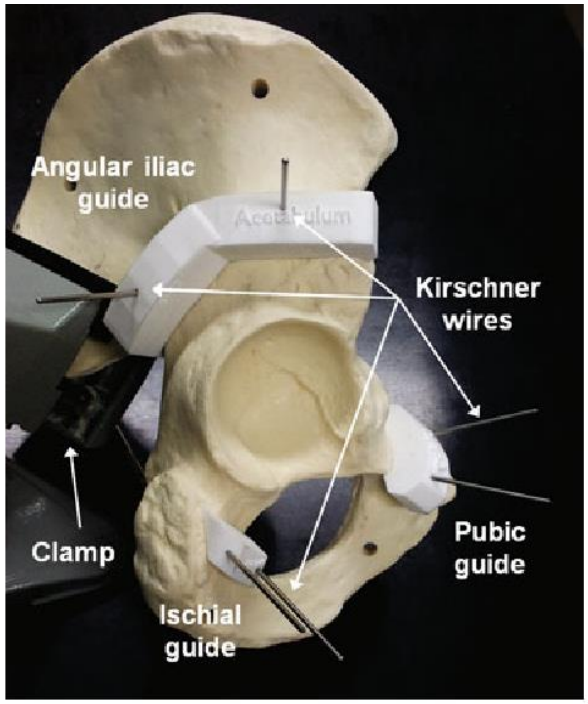

Figure 1: Clamping of the pelvic bone model during the cuts and pinning of the patient-specific instruments with Kirschner wires

Selection of a rapid prototyping fabrication technique for printing surgical jigs and fixtures is dependent on the availability of the technology as well as cost and time. The most common types of medical rapid prototyping technologies reported on are stereolithography, FFF, extrusion-based bioprinting, selective laser sintering as well as material jetting techniques (Tappa and Jammalamadaka, 2018). Post-processing of 3D printed CSGs prior to use in surgery involves removal of printing support structures which, depending on application, can affect the matching of the base with the patient's anatomical surface with the part as well as a suitable method of sterilisation which depends on the material used to produce the part (Winder and Bibb, 2005). While the use of biocompatible metallic materials fulfils many of these aspects, there are some medical grade polymers currently available for use in medical rapid prototyping technology applications where, quality, strength and durability are demonstrated (Wang *et al.*, 2014; Chan *et al.*, 2016). Research into improving medical-grade polymers for 3D printing applications remains ongoing. Current commercially available medical-grade polymers for 3D printing applications are summarised in Table 2 (Dahake *et al.*, 2016; Ligon *et al.*, 2017). The actual fitting of 3D printed surgical jigs and fixtures during surgery is generally carried out using traditional tools such as monocortical and titanium screws, Kirschner wires and Steinman pins (Fu *et al.*, 2013; Hanasono and Skoracki, 2013). 3D printed surgical jigs and fixtures are unique in that they allow for the production of complex and intricate geometries as well as compact and accurate fit on the surface of the anatomy. In some cases, 3D printed CSGs are designed to fit snugly onto the patient's anatomy without the need for screws and fixtures. Incorporation of CSGs into modern surgical practices through the medium of virtual surgery planning have reported reduced operative timeline as well as a higher level of surgical precision and accuracy (Van Brussel *et al.*, 1997; Iii, Rannar and Hirsch, 2012; Fantini, De Crescenzio and Ciocca, 2013; Polley and Figueroa, 2013; Artiaux *et al.*, 2014; Berrone and Tos, 2015; Khan *et al.*, 2016).

Table 2: Commercially available 3D printing techniques and their associated materials used in surgical guide applications.

Commercial Technique	Process	Material
SLA (1987)	Photo-curing	Acrylate
SLS (1991)	Sintering of polymer powders	Polyamide
FDM (1991)	Melt Extrusion	ABS, PEEK, polyurethane foams
MJ (1998)	Ink-jet/poly-jet printing	ABS, PMMA, Acryl, polyamide
Robocasting (2016)	Paste extrusion AM	Silicon nitride

Source: (Negi, Dhiman and Sharma, 2014; Dahake *et al.*, 2016; Koslow, 2016)

There is a growing consensus that the use of custom jigs in improving orthopaedic reconstruction, particularly in the field of oncology. There is evidence that techniques utilising custom jigs result in more accurate fitting between a custom implant and host bone compared to the traditional freehand method which requires mitigation of alignment errors created by reliance on anatomic landmarks for the positioning of the guide or fixture. There are a wide variety of areas for which custom surgical jigs and fixtures have been applied including dentistry (Ganz, 2005; Ito, 2006; Kim *et al.*, 2007; Sohmura, Kumazawa and Cam, 2010; Kashani *et al.*, 2012; Giacomo *et al.*, 2014; Paek *et al.*, 2014), craniomaxillofacial surgery (Poukens, Haex and Riediger, 2003; Bibb *et al.*, 2009; Schepers *et al.*, 2012), total hip and knee arthroplasty (Ng *et al.*, 2012; Kerens *et al.*, 2013), corrective osteotomy (Dobbe *et al.*, 2013, 2014; Holzapfel *et al.*, 2014), bone tumour resection and allograft reconstruction (Bellanova, Paul and Docquier, 2013). Other applications have been reported including orbital implant placement (Hirao *et al.*, 2014) and even neurosurgery as guides for performing brain biopsies, brain tumour resections, custom implantation systems for deep brain stimulation electrodes (Ding *et al.*, 2013) as well as placement of ventricular shunts (Konrad *et al.*, 2011; Huang and Zhao, 2016).

Osteosarcoma resection surgery is a procedure that involves initial removal of cancerous tissue within the confines of an oncologically safe margin followed by defect reconstruction utilizing a customised prosthesis. The overall objective is to treat the disease while maintaining a high level of functionality for the patient. The procedure is complicated and utilises large computer navigation systems that require additional operational personnel in the theatre (Wong *et al.*, 2012; Zhang *et al.*, 2015). A 2012 study by Wong et al. attempted to simplify the procedure for femur osteosarcoma resection surgery and reconstruction via a custom prosthesis (Wong *et al.*, 2012). A 3D CAD preoperative model of the affected femur enabled the generation of a custom surgical cutting jig by FDM 3D printing. This Jig could be placed in a desired orientation that matched that of the custom prosthesis precisely. Ceramic femoral bone models were also 3D printed to test initial positioning of surgical jigs. The method was first validated on cadaveric femurs and took the operating surgeon one minute in total to set the location of the jig and a further three minutes to perform the bone resections via cutting slits incorporated into the jig compared to a reported 24–28 minutes for the traditional navigation-guided approach. The method was then tested on a 46-year-old man diagnosed with low-grade osteosarcoma of the left distal femoral metaphysis. Reported dimensional differences between the achieved and planned bone resection was less than 1mm and were comparable to that of an experienced surgeon with a navigation system. Overall, this study showed that intraoperative incorporation of virtual surgery planning and custom surgical jigs may facilitate and expedite bone resection along a desired orientation, resulting in an accurate prosthesis reconstruction with enormous reductions in procedure time.

Cartiaux et al. reported on the surgical accuracy of 24 surgeons in performing a pelvic tumour resection on a synthetic 3D pelvic bone model compared to the traditional free-hand technique (Artiaux *et al.*, 2014). Generally, in real-time surgery, pelvic bone tumour resections are difficult due to the complex geometry of the pelvis, limited visibility and restricted working space in the pelvic region. The 3D model was imaged from a patient using a CT-scanner. The set of images was reconstructed in 3D and resection of a simulated periacetabular tumour was defined with four target planes (ischium, pubis, anterior ilium, and posterior ilium) with a 10-mm desired safe margin. Patient-specific instruments for bone-cutting were also designed based on the fitting the morphology of the model and the resultant STL file was sent away externally to be rapidly prototyped from polyamide material using FDM 3D printing technology with a dimensional tolerance of 0.2 mm. The instruments were equipped with 2 mm-diameter holes to be pinned on the pelvic bone using Kirschner wires. It was noted that more accurate mapping of bone beforehand is necessary to ensure better contact points. Overall the planned surgical margin for the exercise was given as 1 cm. While the achieved, surgical margins were subject to statistical variation the standard deviation of the 1 cm surgical margins was decreased by use of the synthetic bone model, compared traditional variation technology methods.

Khan 2013 showed that CAD/CAM produced surgical jigs improves the accuracy of primary bone tumour resection, enabling a surgeon to reproduce a given preoperative plan reliably and consistently (Khan *et al.*, 2016). Jigs were fabricated using FDM 3D printing and ABS based resin. Surgery was performed on six matched pairs of cadaveric femurs with a joint-sparing, hemimetaphyseal wide resection precisely outlined on each femur. The resection was performed on each pair using the standard manual technique on one and the custom jig-assisted technique on the other. Superimposition of preoperative and post-resection images enabled quantitative analysis of resection accuracy. The mean maximum deviation from the preoperative plan was 9.0 mm for the manual group and 2.0 mm for the custom-jig group demonstrating the increased accuracy achievable for 3D printed custom jigs. Building on this, using a 3D model of patient's bone constructed from CT/MRI scans an algorithm was developed, to determine a minimal surface area that would provide for stable contact between a customised jig and a bone (Zhang *et al.*, 2015). Once the accurate point of contact was established the jig was fabricated by means FDM. The increased accuracy achievable with the custom jigs will continue to allow for new surgical advances in reconstructive orthopaedic surgery. Validation and broader application through further studies will facilitate the acceptance of 3D printed custom jigs as surgical tools.

4. Summary

The geometric freedom of 3D printing and its rapid individual production capabilities at relatively low cost, provide significant benefits to the medical community. Amongst the different faculties of medicine, orthopaedics has been the first discipline to embrace the technology fully. 3D printing has demonstrated its potential to revolutionise a range of orthopaedic medicine aspects including 1) eliminating the traditional time consuming and labour intensive method of prosthesis manufacture, 2) enabling precise prosthetic implants which are individually tailored to the patients anatomy, 3) removing the need for inter-operative implant manipulation, currently widely required to achieve suitable implant fitting and, 4) facilitating preoperative planning and preparation for surgical procedures. Furthermore, 3D printing is highly amenable to the integration of additional technologies which address significant concerns including postoperative infections prevention and enhancement of tissue implant adherence. Rising geriatric populations throughout the world are requiring increasing numbers of orthopaedic surgeries and more complex orthopaedic interventions. 3D printing supports the advancement of orthopaedic technologies, enabling the rapid development and refinement of prosthetic manufacturing, the generation of innovative, intricate skeletal replacement parts and the progression of surgical techniques.

A broad range of polymers has been developed for 3D medical printing of polymers and composite materials demonstrated as suitable for orthopaedic implants. 3D printed microarchitecture using these materials have been shown to exhibit physical properties which are similar or approach those of natural bone, making 3D printing a viable solution for low cost, accurate and rapid production of bespoke implants. The use of osteoconductive and antiinfective materials have been demonstrated to improve patient outcomes. Continued 3D orthopaedic implant printing research collaborations in conjunction with 3D printed tissue engineering and regenerative medicine promises to facilitate the development of further health care advancements. Given the rapid uptake of 3D printing within Orthopedics, as well as the continuing research advancements in materials science and related medical disciplines, assure a positive future for 3D printing technologies within the broader medical profession. The many benefits compared to traditional orthopaedic methods underline the pivotal role 3D printing is set to play in the future of orthopaedic medicine.

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