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A Review on 3D Printed Bioimplants

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KEYWORDS : 3D printing, Addictive Manufacturing, Bioimplant

Addictive manufacturing (AM) also known as 3D printing have been making inroads into medical applications such as surgical models and tools, tooling equipment, medical devices. One key area researchers are looking into is bioimplants. With the improvement and development of AM technologies, many different bioimplants can be made using 3D printing. Different biomaterials and various AM technologies can be used to create customized bioimplants to suit the individual needs. With the aid of 3D printing this could lead to new foam and design of bioimplants in the near further. Therefore, the purpose of this review articles is to (1) Describe the various AM technologies and process used to make bioimplants, (2) Different types of bioimplants printed with AM and (3) Discuss some of the challenges and future developments for 3D printed bioimplants.

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1 Introduction

Shortage of donor organs remains as a major concern in the medical field and researchers are constantly brainstorming for new ways to mimic or even replicate organs [7]. One of the solutions that researchers have come out with is the use of Bio-implants. A bio-implant is an implant with a biological component that is placed in a cavity of the human body for a period of 30 days or more [9] . It aims to restore, support or enhance the functions of the human tissues by maintaining the compatibility and conformity with the tissues along with the acceptability by the body, the strength of materials and the intactness of the implant [1]. However, much effort is required to make implants that are of complex geometry and custom fitted for individual patients through traditional cutting, forming and casting methods such as Computer Numerical Control machining. Thus, this leads to the rise of Addictive Manufacturing (AM) which is a manufacturing technique that adds rather than subtracts material. The ability of AM technology to produce actual functioning parts is also a contributing factor to its newly acquired popularity. However, this technique is still in the developmental phrase and more has to be done to explore its maximum potential [10]. A survey done in 2012 by Wohlers associates, showed a growth in products and services directly associated with AM process worldwide. Numbers rose by 28.6% from $1.714 billion in 2011 to $2.204 billion in 2012. Medical and dental sector has established itself as a strong sector with 16.8% market share in AM and making it the third largest sector for the 12th year running (Fig. 1) [2]. AM technologies have made inroads in medical applications ranging from non-customised, off the shelf implants to customised implants and prosthetics, customised models for surgical planning to personalized instruments for surgical processes. Several products made with AM processes have received regulatory clearance [2].

This review plans to introduce various AM technologies used for manufacturing of bioimplants, classification of different bioimplants and finally a

discussion of the possibilities of improved AM technologies leading to next generation of bioimplants.

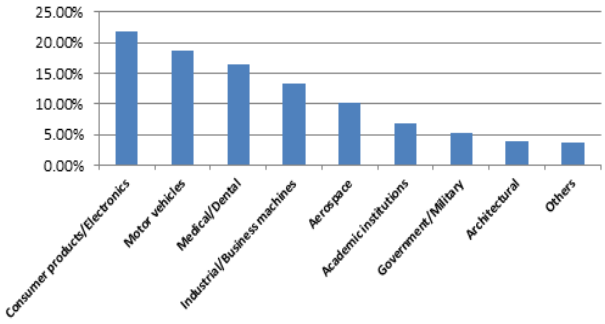


Fig. 1 AM market share of different industries. Medical/Dental is ranked Number 3. Figures taken from [2].

2 Addictive Manufacturing (AM)

Addictive Manufacturing (AM) also known as rapid prototyping (RP) technologies or 3D printing consists of different automated fabrication. The AM process consists of design modelling and production. 3D models can be designed by 3D CAD software or obtained through CT scan or MRI. After which, the file is converted to a STL (stereolithography) file or the new AFM format and sliced into series of 2D cross-sectional layers, creating a computer file showing the path for the printer to take for tracing [11]. The process is usually done bottom up. Depending on the AM technology, parts may or may not have to be post processed to obtain the finished product.

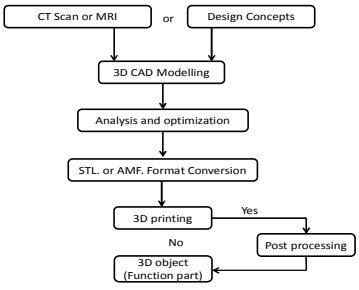


Fig. 2 Brief schematic diagram of product development cycle for 3D printing of bioimplant

The ability of adding materials leads to a shorter manufacturing time and enables the production of complex patterned objects [12] of small volume which was previously uneconomical due to the complexity of the manufacturing process. Other advantages include customisation, lower cost, lesser tooling machines and little technical expertise required to operate machines [13]. It is important to note that build times varies, depending on the machine and technology used. Materials may also play a role to get the final resolution. Even though AM possesses many advantages; it still has some disadvantages such as pre- and post- processing requirements, limited amount of printable materials and high equipment cost. However, researchers have been working on the disadvantages by developing new methods and materials [14], this will be mentioned in chapter 4.

2.1 AM Technologies in Medical industry

There are currently many different AM technologies used for making bio-implants such as Inkjet Printing (Polyjet), 3D printing (3DP), Stereolithography (SLA), Selective Laser Melting (SLM), and Bioprinting which is another category by itself. They are classified by various ways such as the type of energy source used or the production process etc. For this paper, we will classify them based on the ability to print biological materials (Fig 3): (i) directly or (ii) indirectly.

i. Directly – prints support structure and biological materials (cell, DNA, proteins) together, also known as Bioprinting.

ii. Indirectly – prints support structure only.

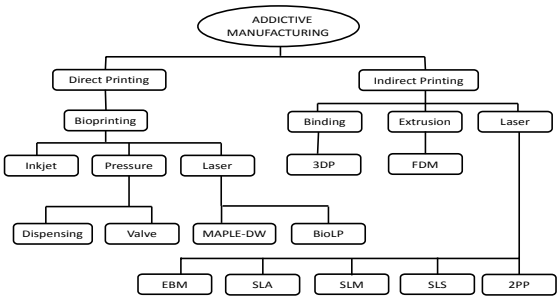


Fig. 3 AM technologies based on the classification mentioned and method to form the structures.

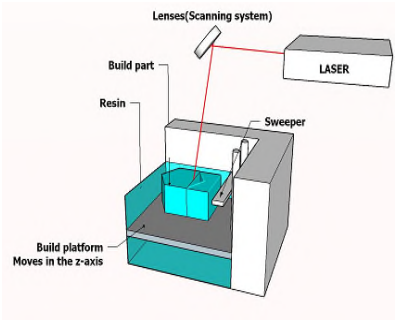
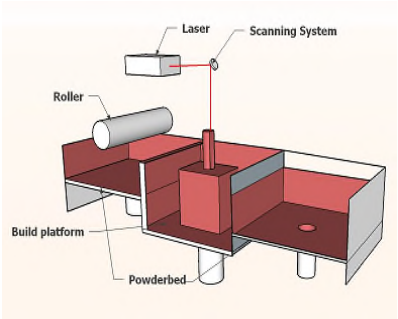
There are various AM technologies competing in the market, each with its own pros and cons. For more information on other technologies available, do refer to other good reviews and books [12, 15].

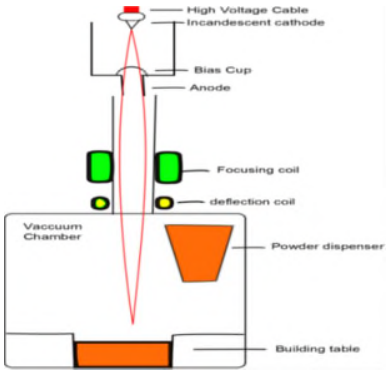
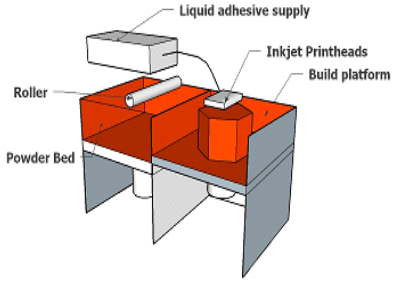
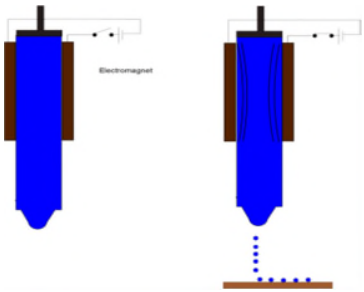
2.1.1 3D AM technologies

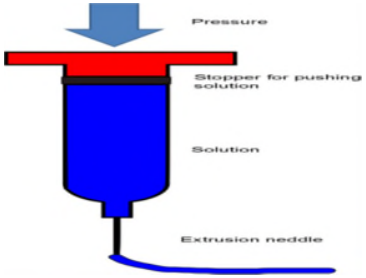
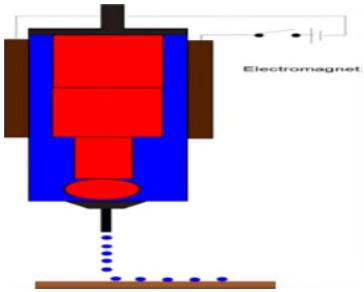
Most technologies discussed here are established manufacturing techniques that have been around for quite some time. Indirect printing technologies do not print biomaterials. Such methods are used mainly for the construction of scaffolds which are then used for the seeding of cells, drug delivery systems, potential biochips or biosensors. However, it is important to note that each technology has its own limitations and applications. Some

technologies such as SLA and polyjet inkjet-based systems use ultraviolet (UV) or white light to cure liquid materials while others use laser to melt or soften materials for joining (SLS, and SLM) and some like 3DP uses binding materials such as glue to stick the materials together. To make microstructures such as the "lockyballs" interlock micro scale scaffold to hold cells inside the two photon polymerization is used [16]. AM technologies have shown to be extensively involved in the fabrication of tissue engineering structure with its ability to provide precise control over both external macrostructure and internal microstructure of scaffolds shown by many review papers [12, 17-19]. Although complex geometry can be achieved with indirect 3D printing, cells are still seeded secondary. Therefore, problems such as the inability to replicate a multi-cellular structure arise [17].

Direct bioprinting have been gaining huge interest in the field of science as there is a need for accurate control of cell position and tissue architecture in 3D constructs with micro-scale precision. Currently, there are three main ways that cells can be printed on the implants directly, (i) Inkjet, (ii) Extrusion and (iii) Laser Assisted Based (LAB). Many commercial printers are currently available such as NovoGen MMX Bioprinter™ and regenhu BioFactory® which combines the different methods such as different nozzle heads (inkjet or Extrusion) where multiple cell types and biomaterials can be directly placed in specific spatial arrangements. There are three key components of any LAB technique are a pulsed laser source, a target plate (Quartz ribbon) and the biopolymer hydrogel or cell suspension. Two widely employed variation: Matrix-assisted pulsed laser evaporation direct write (MAPLE-DW) and Biological laser printing (BioLP) which are distinguished by the nature of the ribbon. More information on laser assisted based technique can be found in [20]. Table 1 below describes the some methods of AM technologies currently used for bioimplant fabrication, while comparing the advantages (Adv) and Disadvantages (Dis) and resolution of the parts when made from the different AM technologies. Application shows the implants that have been make without additional tooling.

AM technology	Brief Description	Cell printing	Materials	Resolution (μm)	Adv	Dis	Application (Ref)
SLA & 2PP 	• Use of laser to trace the 2D cross section layer • Once layer is done, build platform lowers down, for the next layer • Process repeated till product is done	Yes	Photocurable resin/polymer	0.5 to 50	High accuracy with complex internal features	Single material; requires photopolymers	SLA Hearing aid shells [21], Hemi knee joint [22], patient skull for casting [23], tooth/denture [24, 25] 2PP lockyballs [16] , Ossicular (bone in the middle ear) prosthetics [26]
SLM 	• Use of laser to trace the 2D cross section layer • Once layer is done, build platform lowers down, for the next layer • Process repeated till product is done	No	Metal alloys powders, ceramic powders	20 to 100	High strength; Full dense parts, high resolution	Post processing. Metal parts only	Bone scaffolds like Hip joint [21], facial [3] and cranial [27] Dental application (denture) [6, 28-31]
SLS	Similar to SLM expect sintering of powder instead melting the powder to join the material together	No	Thermoplastics, ceramic powders and metal powders (required additional binding material)	50 to 100	No support design required, large part size; variety of materials	Required post processing due to powdery finish	Bone scaffold (hip joint, knee) [8, 21, 32], Dental application (denture) [6]

EBM 	• Similar process to the SLM • Electron beam is used to melt the metal instead of a laser • Electromagnetic coils help to control the electron beam	No	Metal powder (ie titanium alloys)	50 to 200	Fast build rate; full dense parts	Limited materials available, post processing	Bone scaffold such as hip stems [33] and vertebral bodies [34]
3DP 	• Inject head dispensing adhesive to trace to 2D cross section • Once layer is done, build platform lowers down, for the next layer • Process repeated till it is complete	No	Powder and specialize binding liquid	50 to 100	Multiple materials available	Extensive optimization required to get finish product	Biofunctionalised Bone scaffold with drug releasing functions [5, 35], ear cast [36]
Inkjet 	• Inject head dispensing biomaterial in droplet form • Droplet size is control by piezoelectric or thermal	Yes	Cell suspension	20 to 100	Low cost; fast build rate, multiple materials	Viscous solution may clog system	Soft scaffold patterning of C2C12. PC12, Smooth muscles cells, Human fibroblast and bovine aortic endothelial cells [17, 37], Cartilage [38]

Extrusion/ Dispensing 	• Pressure is used to force material out of the needle • Material release in filament form • Solidification through physical or chemical means	Yes	Hydrogels, viscous materials	150 to 300	Simple process	Low build rate extrude out as filament only	Soft scaffold patterning of human fibroblasts and bovine aortic endothelial cells Liver construct [17, 37, 39-41] heart or vessels constructs [4, 42, 43]
Valve 	• Pneumatic Pressure used for dispensing • Small valve controlled mechanically, electrically or magnetically for the flow of material • Material release either in droplet or filament form	Yes	Hydrogels, viscous materials	100 to 200	Higher accuracy compare to extrusion	Viscous solution may clog system	Soft scaffold patterning of rat bladder cells or cell microarrays [17]
Laser (Biological Laser Printing (BioLP)	• 3 components: pulse laser, target plate (quartz ribbon) and hydrogel or cell suspension • Quartz ribbon with a thin metal layer absorbed laser pulse	Yes	Hydrogels, viscous materials	10 to 100	High speed and accuracy, single cell manipulation	Homogenous ribbons needed, no structural support need high viscous materials	Soft scaffold/patterning of Chinese hamster ovary, human osteosarcoma and rat cardiac cells [17, 37] Skin and heart constructs [44-46]

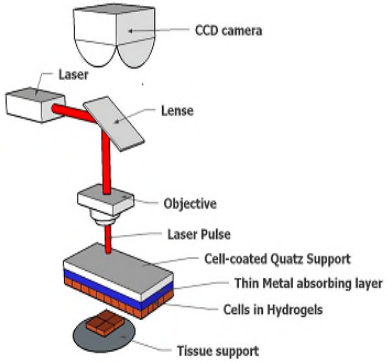
	• Thermal expansion of the layer cause a release of hydrogel or cell suspension

Table 1 Characteristics of AM technologies that are used for making bioimplants

3. BioImplants and 3D Printed Implants

AM technology is useful for the fabrication of bioimplants as such implants of complex geometry, possess individual specific requirements and are usually produced in low volume [14, 47]. Furthermore, with the improvement in Reverse Engineering (RE) technologies such as Computed Tomography (CT) scans, Magnetic Resonance Imaging (MRI) and 3D laser scanning; implants can be customised to each individual specific need. This has allowed AM to gain huge interest in the medical field as customisation using AM technology saves time and money. AM have been used in many medical applications and can be classified into the following categories based on Giannatsis 2009 [10]:

- Biomodelling – fabrication of physical model for better visual in surgical planning or explanation to patients
- Design and fabrication of customised implants that offer better fitting to patients for prosthetics, rehabilitation and plastic surgery
- Fabrication of porous implants (scaffolds) and tissue engineering
- Fabrication of specific surgical aids and tools
- Drug delivery and micron-scale medical devices

Biomodels are models of different parts of the human anatomy that are fabricated. One of the first major applications of these biomodels was as an aiding tool for surgical planning and rehearsal [11]. Every patient is unique and surgeons are required to understand his/her anatomy before the operation. Previously, only CT/MRI images are available to surgeons in aiding them to understand the patient's anatomy. Thus, by having a physical biomodel, surgeons are now able to better visualise and this will aid them significantly in the planning of surgery procedures (ie reducing the risk of misinterpretation). Possible rehearsal and simulations before surgery can become an option and they would also be able to use the physical biomodel as a communication tool to help patient better understand the operation details. Another huge potential aspect of addictive manufacturing will be the construction of human specific implants due to its ability to construct complex geometry, promote tissue regeneration and control release of biomaterials. As the name suggested, bioimplants for medical-clinical applications such as porous implants, prosthetics, drug delivery and biosensors can be describe as implants since they are usually most or less implanted into the body for long periods of time. There are three types of bio implants and can be classified as (i) Biological implants, (ii) Biologised implants and (iii) Biofunctional implants [1]. The difference between the three classifications is mainly due to the amount of cellular components that make up the implants shown in Fig. 4.

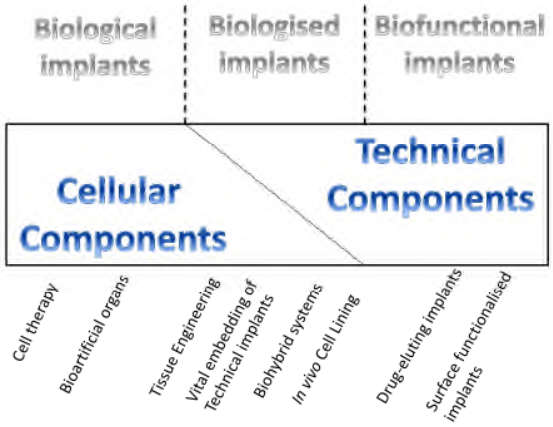


Fig. 4 Categories of Bioimplants followed by the components and examples

3.1 Biological implants

Biological implants are manufactured from biological materials such as cells, protein etc using bioprinting. These implants can be considered as organ printing as ideally autologous cells are being used to reject the chances of rejection by the body and also to reduce waiting time for the replacement organ. Usually two key components are needed for making biological implants, firstly a bioprinter (mentioned in previous section) containing materials such as living cells (ie stem cells or tissue spheroids and biodegradable scaffolds/matrices (hydrogels) which predetermine the 3D form for creating the organ. Secondly, a biochemical reactor in which the manufactured organ can mature in vitro. Organ printing is defined as a computer aided process in which cells or cell-laden biomaterials are placed in the form of aggregates, which then serve as building blocks and are further assembled into a 3D functional organ [48]. The ability to mimic the organs by accurately placing multiple cell types at its specific location may offer the possibility of manufacturing patient specific organs commercially. This usually involves integration of three areas (i) Functionality of the cells to ensure the cells are performing their specific role (ii) Production of the organ or tissue by combining cells and 3D scaffold using biofabrication techniques (iii) Characterisation of the biofabricated construct to focus on the issues of immunology, toxicity and ability to remain its form after post implantation [48]. Although organ printing shows huge potential as mentioned those three key technologies still have to be addressed. There is currently no biological implant available. However, there have been few examples showing how much organ printing has advanced. The printing of heart vessels and tissues [4, 42], cartilage [38] skin [44] and liver tissue [39] are some of the organs in the works.

Forgacs and team from the University of Missouri were able to print blood vessels with bioprinter using the extrusion based methods [4, 42] shown in figure 5. A combination of cardiac cells and endothelial cells was printed on a collagen gel paper/hydrogel which as a support. With the addition of VGEF, an endothelial mitogen and vasculogenic stimulator and the self –organizing capacity of the cells ensures that vascular network formation [42]. Another group was able to develop another method for scaffold-free, multi-layered bioengineered small diameter blood vessels. Vascular grafts made up of primary human adult aortic smooth muscle (HASMC), endothelial cells (HAEC), and dermal fibroblasts (HDF) were printed using in cellular cylinder and layer by layer build up with supporting building blocks aligned by the printer. Cellular cylinder were then allowed to fused overnight before putting in the bioreactor [43]. Cell-based therapy has been looked into by many researchers for it abilities to sense diverse signals, move to specific sites in the body, integrate inputs to make decisions, and execute complex response behaviors—all in the context of a specific tissue environment. Researchers from University of Rostock were able to develop a cardiac patch with the used of the Laser-Induced-Forward-Transfer (LIFT) cell printing technique. Human umbilical vein endothelial cells (HUVEC) and human MSC (hMSC) is printed onto the patch in a defined pattern for cardiac regeneration. Results shown in animal testing were quite promising with increased vessel formation and significant functional improvement of infarcted hearts of rats [46].

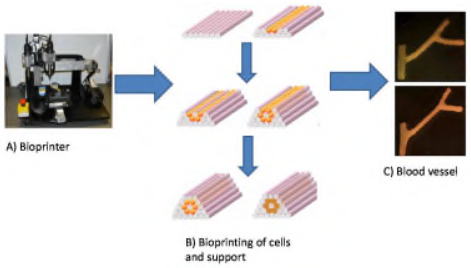


Fig. 5 Bioprinting of blood vessels. A) Bioprinter loaded with cells and support B) Printing and patterning of support (purple) and cell (orange) in filament form C) formation of blood vessels. Picture adapted from [4]. Reproduced with permission of IOP Publishing.

The need for skin replacement from burns, skin diseases and other causes have seen many great advances for creating tissue engineered skin for over the last 25 years [44]. 3D printed skin can now be added to this repertoire as well. Lothar Koch and team have shown using the Lift technique as well, mesenchymal stem cells (MSCs) or skin cell lines (fibroblasts/keratinocytes) can be printed without any damage to the cells [44, 45].

Another organ that has been widely studied in the area of bioprinting is the liver. Organova (http://www.organovo.com/) one the manufacturer of the biopotter promised the possibility of printing a functional liver by 2014. This might seem achievable as Robbins *et al.* has successfully used the NovoGen MMX Bioprinter™ (Organovo Holdings, Inc., San Diego, CA, USA) to print metabolically active 3D hepatic tissue. They demonstrated increased liver specific function of the tissue for up to 135 hours compared with matched 2D cell cultures [39]. Furthermore, compartment-specific organization and functionality in a rudimentary microanatomy was shown for hepatocytes, hepatic stellate cells and endothelial cells. Sun and his group used the solid free-form fabrication technique to print alginate-encapsulated HepG2 cells, growth factors and scaffold materials in an organized 3D architecture [40]. These micro-organs were dynamically micro-perfused to mimic an *in vivo* scenario for drug metabolism studies. As a follow-up, the authors used this system to perform a radioprotection study on liver cells [41].

Although currently there are no functional organ printed but as technology and research advances we might be able to see it sooner rather than later.

3.2 Biologised Implants

Biologised implants are made of a combination of cellular components and permanent biomaterials. The difference between biological implants (mentioned previously) and biologised implants are the degradability of the 3D structure. Biologised implants structures are permanent and non-biodegradable. The permanent biomaterial structures are biocompatible and provide the mechanical stability for cellular colonisation. As such one application of AM technology is the construction of customized biologised implants for reconstructive and plastic surgery. Medical imaging techniques such as MRI or CT scans can be converted directly to STL. file which can be send to AM machines for direct printing of the patients implant. This can lead to significant time savings and better accuracy and quality in surgical operations. Most biomaterials involved in the implants are Bioinert (materials that do not react with the body - implant covered in a thin layer of mucous membrane). For example, stainless steel, tantalum, gold, titanium, nitinol, inum and aluminium oxide ceramic. This section will focus on orthopaedics and dental implants mainly made from metals and using indirect printing methods. Traditionally, AM techniques were used to develop molds for casting which can be seen in hemi knee joints [22], skull [23] and dental products [24]. However, like mentioned with the improvement of AM technologies, functional parts can now be printed directly.

Orthopedics (relating to the deformities of bones or muscles) is a prominent area for bio implant. Bone regeneration, soft tissue regeneration, spine, bone cement etc. are various applications associated with it. They include both the temporary implants screws and plates and permanent ones that are used to replace knee, hip joints. One key material used is Ti6AlV4 alloy high tensile strength, light in weigh, corrosive resistance and ease of fabrication of shapes. Researchers at Helsinki University Central Hospital were able to develop a medical workflow for the use of 3D printing for reconstruction of facial defect [3]. With the help of the SLM machine, Ti6AlV4 implant was printed and fitted into the patient. AM technology allows them to have an exact fit of the implant, reduced surgery time leading to reduce the risk of complications and patient morbidity [3]. Although hip stems are successful, the average lifespan is about 10 to 15 years depending on the patient. Other factors such as implant type, fixation method, and material used for the implant could also determine the lifespan of the implant [33]. Bone remodelling occurs to meet the demands of mechanical loading by bone ossification and bone reabsorption. Implant designers have to ensure stress shielding does not occur in the patients due to the mismatch between the stiffness of the prosthetic stem and the patient's bone [33]. Using EBM, Harryson [33] was able to fabricate a Ti64A14V hip stem implant with a mesh structure aimed at lowering the bend modulus to reduce stress shielding and uneven bone remodelling. The FEA results indicates in the proximal portion of the femur that an even stress distribution can be obtained with the lowering of the bend modulus of the stem. As a result, bone remodelling will be reduced. Other implants that researchers have been looking into: SLS for cranial [27] and EBM for vertebral bodies [34].

The process sculpting a wax ear cast for use when making a definitive prosthesis for a patient who has had auricle ablative surgery is challenging. A skilled anaplastologist along with complex instrumentation are required to perform facial laser scans and reproduce anatomic details [36]. Ciocca (2004) [36] and Mardini (2005) [49] showed that by using a 3D laser scanner and different AM technologies 3DP for the first and inkjet print for the latter, they were able to get molds to form the pinna. Its show that data acquisition and elaboration is less time-consuming and expensive than with previously described methods or fabricating the wax prosthesis manually. Surface data may be corrected and adapted to more accurately reconstruct the prosthesis.

Most dental implants and many other orthopaedic implants are now made of titanium and its alloys. The use of AM technologies for dental applications has a huge potential due to the complex geometric involved, low volume and the need of personal customization [50]. Denture process done by [24], partial denture [25], teeth wax model [51] for indirect application. The framework for used of SLS and SLM for direct application of dental prosthesis for stainless steel, Ti6Al4V CoCr-alloy was done. Other studies for SLM for dental applications were further studied [28-31]. A lot more in rapid prototyping for dental application can be further explored through additive manufacturing. Fig. 6 shows the different Biologised implant made from EBM, SLS and SLM

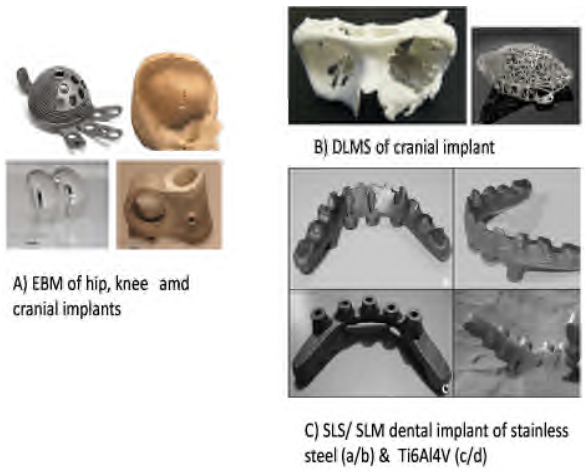


Fig. 6 Metals implants made from A) EBM picture courtesy of Arcam B) DMLS [3] Reproduced by permission of Emeraldinsinght and C) SLM/SLS [6] Reproduced by permission of Taylor & Francis

3.3 Biofunctionalised implants

Biofunctionctionalised refer to the field of surface treatment with the purpose to optimally use the surface for life science applications [1]. This means that after implantation, bioactive surfaces of biofunctionctionalised implants interact with the biological environment in the body. The development and application of customised properties of the base materials required. The materials for Biofunctionalised implants are usually bio-active. Bio-active materials refers to materials that integrates into the organism without capsule formation and develop a permanent bond and materials includes glass ceramics, hydroxyapatite and glass ionomer cement.

As described earlier, the used of AM technologies and bioactive materials can lead to fabrication of implants with special geometrical characteristics like scaffolds for the restoration of tissues. The use of 3DP of scaffolds from hydroxyapatite or tricalcium phosphate (TCP) was shown to be able to improve cell proliferation and spreading when compare to current commercial products such as bone replacement material BioOss® [5]. The used of SLS to sinter different bioactive glass can also be seen [8, 32].

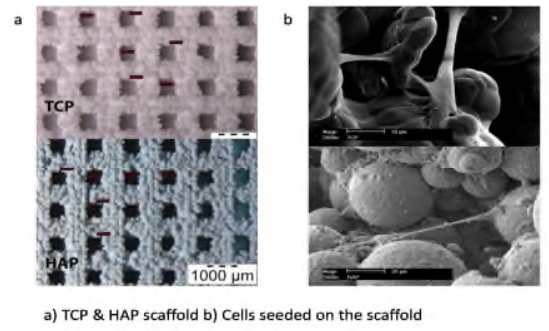


Fig. 7 Biofunctionalised implants for bone scaffolding using (a,b) TCP & HAP [5] Reproduced by permission of Wiley and c) Bioglass [8] Reproduced by permission of IOP Publishing

Beside the making of scaffolds, other customised microsystems and therapeutic devices for controlled highly specific and precise drug delivery can also be made with AM [10]. By using AM technology such as SLS, the pore size and micro-features of can be incorporated in the PLA or PMMA scaffold, allowing the release of drug in a controlled manner [52, 53]. However, over the years more different materials have been developed and adapted of AM technologies to print. Using 3DP, Elke and team were able to print simultaneous geometry with hydroxypropylmethylcellulose (HPMC) and tricalcium phosphate (TCP), localized organic bioactive loading (recombinant bone morphogenic protein 2 (rhBMP-2), heparin (a model polysaccharide), and vancomycin (an antibiotic glycopeptide), and localized diffusion control [35]. Using the 3D bioplotter, Mesoporous bioactive glass (MBG) can also be printed [54, 55].

4. Current challenges and Future Directions

Advancement in addictive manufacturing machinery, materials, imaging, nanotechnology and related field such as information technology for computing, modeling and simulation have led to a transformation of life science and a whole new world of possibilities in the way scientific research can be conducted [56, 57]. Areas such as addictive manufacturing will require not only collaborations among different researchers but an integration of different disciplinary approaches which were once viewed as separate and distinct [12]. Melchels also foresees the convergence of skills and techniques so as to bring AM to higher levels [12]. Currently 3D printing for bioimplants especially for soft tissues is still in the initial stage. Researchers are looking into many areas such as materials for biocompatibility and printable. A lot of research still has to be done to get the optimal bioimplant. In this section, more will be elaborated on how improvements in AM technologies are useful for the development of better implants to improve patients' lives.

4.1 Biomaterials

Currently, AM technologies have its pro and cons, particularly with biomaterials. Even though there are many materials available, not all are biocompatible and not all biomaterials are available for the used with AM technologies. Many scientists and engineers have been researching on different materials and processes in attempt to develop new biomaterials or to improve on existing materials for printing.

In order to address these needs, Bens and team developed a new photopolymer resin for the SLA which is less-toxic and is able to mimic both soft and stiff technical plastics depending on the formulation. It is of sufficient low dynamic viscosity, high process speed and good accuracy when compared to other acrylic resin materials such as PP, PE or ABS [58]. Thus by adjusting the formulation, different mechanical properties can be obtained. This saves cost as the need to purchase different polymer is no longer necessary. Iron-based alloys are being studied due to its property of high strength and slow corrosion. Current fabrications generated from Fe-based raw material must be machined into their desired form. Recently, Chou [59] from the University of Pittsburgh was able to fabricate craniofacial scaffolds using inkjet printing with Fe–30Mn (wt.%). This opens another possible option for doctors who require bone scaffold with similar mechanical tensile properties as natural bone but degrade quicker as compared to the use of pure iron [59].

Another new potential material for 3D printing could be the use of graphene. Graphene is an atom-scale carbon sheet with a honeycomb-lattice arrangement which exhibits a unique combination of high electrical and thermal conductivity, high stiffness, tear and abrasion resistance, chemical and thermal stability, gas barrier performance, and absorption of Ultraviolet (UV) and Infrared (IR) radiation [60-63]. Although graphene is a long existing material, it is not until recently that Tolle was able to process graphene making it printable with the use of inkjet printer or bioplotter (extrusion based system)[64]. This may lead to printing new implants with a single material but

posing multiple functional properties. It was also announced that American Graphite Technologies will partner researchers from Kharkov Institute of Physics to further research on ways to adapt 3D printers to print with graphene. With further research into graphene, implants with better sensitivity and functionality may be made possible in the near future. Collin ladd and team were able to develop a process to print liquid metal (alloy of gallium and indium). This ability to print metal in liquid like properties is important for soft, stretchable and shape reconfigurable analogs to wires, electrical interconnects, electrodes, antennas, meta-materials and optical materials at room temperature [65]. This could possibly lead to a new process of printing cells onto metal (multi-materials) at room temperature in the same machine, saving energy and reduce the chances of cross contamination from the multiple transfers from one printer to another for printing different layers and structures.

4.2 CAD software

Reverse engineering (RE) and Addictive Manufacturing (AM) work very well together especially for the production of implants. RE technology enables the scanning of human body parts which has a vital role for developing the 3D model while AM technology is suitable for the production of low volume parts with complex geometry such as the human body tissue or organs. For example, images of bones can be captured by a 3D scanner, CT scanner or MRI system. The 2D image data captured will then be converted into a 3D image. Using the 3D image, a 3D voxel (3D pixels) model can be generated for analysis by a surgeon. Mimics (Materialise NTV) is one of the common commercial software packages available for generating 3D model from MRI or CT scanned images. Once the model is generated, editing or redesigning can be done by other commercial software such as Rhino, Rapidform, Medical modeler etc. Simulation or fabrication can be done on the edited model with AM technologies. More details about the designing process can be found in [14, 47]. One possible problem that users face when designing implants for patients is the software. Although there are many different software available, most software require users to design 3D structures in a 2D plane which is not very convenient. A survey conducted with researchers showed that the lack of proper and competent CAD tools affecting the uptake rate of AM technologies and may hinder their research as well [14]. One way to encourage more utilisation for 3D printing will be to make CAD interfaces easy to use and having pre-defined product scopes that enable end-users to make meaningful product changes within expert designed constraints [14, 66]. In order to exploit the full advantage of AM technologies, one possible method is to integrate process–structure-property relationship into CAD systems [66]. It will be necessary to have computational methods for designing and analysing of materials and their combinations. Multi-scale modelling, inverse design and optimisation methods are needed for these tasks. New CAD systems will be needed to simplify significant complexity or sophisticated technologies for easy decision making and understanding for the user. With improvement of software in the near future, design of implants can be maximised with significantly improved performance that fully utilises materials and efficient manufacturing process, reducing the cost and possibly achieving heretofore unrealizable capabilities [14].

4.3 Hardware

Although AM has many advantages, most commercial AM technologies can only produce parts printed with a single material for the whole process. With the advancement of technology, certain AM technologies such as inkjet printing and extrusion are able to print multi-materials at the same time. This may lead to shorter manufacturing time, cost savings and possible new designs for implants.

As mentioned, there are a few technologies that are able to print multi-materials; one of it is inkjet printing. The commercial printers by Stratasys Inc such as Objet Connex series and Objet1000 PolyJet 3D printers are capable of 3D printing up to 14 different materials in a single build by mixing different ratio of materials while printing. However those materials are mainly made up of variations of rubber and plastic-like options [67]. Using their own system created from 3D inkjet printing, Mustaffa and team were able to direct print an electronic circuit using silver nanoparticles using the inkjet printing system [68] although that was for 2D structures. They also found out when creating 3D multi-material structures using inkjet printing requires arrangement of overlaying the deposited dots in a manner that creates a dense and flat layer pattern [68]. The Technology Partnership (TTP) has announced recently developed a multi-material 3D printer head called Vista which promises to change the shape of 3D printing industry. TTP's Vista reported the ability to 3D print a wide range of both inorganic and organic matter, including plastics, metals, ceramics, enzymes and biological cells [69]. Lately, researchers from the University of Princeton were able to develop a novel strategy to seamlessly intertwined biological cells or tissues with functional electronics via the help of AM technologies [70]. This may lead to the making of new and distinct bioimplants in both form and function enabling possibilities such as direct manufacturing of biosensors and drug delivery system embedded in the implants. Further research on different classes of nanscale functional building blocks such as magnetic, plasmoic and ferroelectric nanoparticles, the interaction between cells and these particles and how the use of 3D printing can aid in patterning or integrating those 2 together, could expand the opportunities for engineering new bionic implants. A novel 3D multi-nozzle

deposition machine that is able to deposit multi-materials with the use of differentnozzle systems. This gives the user the ability to use a wider range of materials to work with however one have to ensure that the different materials can integrate together otherwise the parts may not be done properly [71].

4.4 Automation of Pre and Post Processes

The automation of the production phases (pre & post) could facilitate the progress of bio-implants. To reduce the risk of contamination as most implants will be placed in the body, it would be beneficial to integrate the different stages of production and culturing of tissue and reduce manual intervention and transferring. Using the bionic ear as an example, automation can be done by machines for the cell-culturing phase in a clean room to reduce contamination. After the cultivating the cells, it could be directly loaded into the bioprinter for post manufacturing cultivation of tissue constructs. 3D hydrogels constructs with the isolated cells can be printed in a zone of an isolated system by means of multiple head bioprinter. After the implant is done, with the use of a precision robotic arm, it can be place in the bioreactor immediately for the cells to grow. With the integration of all these different phases, this reduces contamination as it is all done within the same area and if possible with the same machine thus minimizing manual intervention. Another example, using a production line concept, if doctors are able to create the implant straight after getting an image of the patient's anatomy with a click of a button, the images can then be converted into a 3D CAD file and sent to the 3D printer (loading of materials and post processing done by automation). After printing, he is able to check back to ensure the implant is done up properly, all within the same facility. This saves time and cost tremendously and is definitely a significant development in the medical field.

5 Conclusion

In summary, addictive manufacturing will enable the production or fabrication of improved 3D-printed medical implants. 3D printing allows implants to be custom-matched to a specific individual and this review showed that it is used for making better titanium bone implants, prosthetic limbs and orthodontic devices. Also 3D printing can be CAD integrated and stereolithographic models can be prototyped which can be used to manufacture precise complex parts and thus be used in organ implantation. As more inter-disciplinary researchers are recruited into the field together with the advancement in biomaterials, it is likely that AM machines and techniques will be further improved over the years. This may lead to a new generation of implants in terms of form and functionality and the possibility to print your own "organ"

6 References

[1] A. DGBMT, "Postion Paper Bioimplants: Biological, biologised and bio functionalised implants," 2011.

[2] T. Wohlers, *Wohlers Report 2013: Additive Manufacturing and 3D Printing State of the Industry Annual Worldwide Progress Report*: Wohlers Associates, Inc, 2013.

[3] M. Salmi, J. Tuomi, K.-S. Paloheimo, R. Björkstrand, M. Paloheimo, J. Salo, *et al.*, "Patient-specific reconstruction with 3D modeling and DMLS additive manufacturing," *Rapid Prototyping Journal*, vol. 18, pp. 209-214, 2012.

[4] K. Jakab, C. Norotte, F. Marga, K. Murphy, G. Vunjak-Novakovic, and G. Forgacs, "Tissue engineering by self-assembly and bio-printing of living cells," *Biofabrication*, vol. 2, p. 022001, 2010.

[5] P. H. Warnke, H. Seitz, F. Warnke, S. T. Becker, S. Sivananthan, E. Sherry, *et al.*, "Ceramic scaffolds produced by computer-assisted 3D printing and sintering: Characterization and biocompatibility investigations," *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, vol. 93B, pp. 212-217, 2010.

[6] J. Kruth, B. Vandenbroucke, J. Van Vaerenbergh, and I. Naert, "Digital manufacturing of biocompatible metal frameworks for complex dental prostheses by means of SLS/SLM," *Virtual Prototyping and Rapid Manufacturing-Advanced research in virtual and Rapid Prototyping, Taylor & Francis, London*, pp. 139-146, 2005.

[7] M. Lavine, L. Roberts, and O. Smith, "If I Only Had a," *Science*, vol. 295, p. 995, February 8, 2002 2002.

[8] K. C. Kolan, M. C. Leu, G. E. Hilmas, R. F. Brown, and M. Velez, "Fabrication of 13-93 bioactive glass scaffolds for bone tissue engineering using indirect selective laser sintering," *Biofabrication*, vol. 3, p. 025004, 2011.

[9] U. S. F. a. D. Administration. (2014). *IDE Definitions and Acronyms*. Available: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046698.htm

[10] J. Giannatsis and V. Dedoussis, "Additive fabrication technologies applied to medicine and health care: a review," *The International Journal of Advanced Manufacturing Technology*, vol. 40, pp. 116-127, 2009.

[11] P. A. Webb, "A review of rapid prototyping (RP) techniques in the medical and biomedical sector," *Journal of Medical Engineering & Technology*, vol. 24, pp. 149-153, 07//Jul/Aug2000 2000.

[12] F. P. Melchels, M. A. Domingos, T. J. Klein, J. Malda, P. J. Bartolo, and D. W. Hutmacher, "Additive manufacturing of tissues and organs," *Progress in Polymer Science*, vol. 37, pp. 1079-1104, 2012.

[13] J. R. Honiball, "The Application of 3D Printing in reconstructive surgery," Stellenbosch: University of Stellenbosch, 2010.

[14] D. L. Bourell, M. C. Leu, and D. W. Rosen, "Roadmap for additive manufacturing: identifying the future of freeform processing," *The University of Texas, Austin*, 2009.

[15] C. K. Chua, K. F. Leong, and C. C. S. Lim, *Rapid prototyping: principles and applications*: World Scientific, 2010.

[16] R. A. Rezende, F. D. A. S. Pereira, V. Kasyanov, A. Ovsianikov, J. Torgensen, P. Gruber, *et al.*, "Design,

physical prototyping and initial characterisation of 'lockyballs'," *Virtual and Physical Prototyping*, vol. 7, pp. 287-301, 2012/12/01 2012.

[17] C. J. Ferris, K. G. Gilmore, and G. G. Wallace, "Biofabrication: an overview of the approaches used for printing of living cells," *Applied microbiology and biotechnology*, vol. 97, pp. 4243-4258, 2013.

[18] S. M. Peltola, F. P. Melchels, D. W. Grijpma, and M. Kellomäki, "A review of rapid prototyping techniques for tissue engineering purposes," *Annals of medicine*, vol. 40, pp. 268-280, 2008.

[19] W.-Y. Yeong, C.-K. Chua, K.-F. Leong, and M. Chandrasekaran, "Rapid prototyping in tissue engineering: challenges and potential," *TRENDS in Biotechnology*, vol. 22, pp. 643-652, 2004.

[20] N. R. Schiele, D. T. Corr, Y. Huang, N. A. Raof, Y. Xie, and D. B. Chrisey, "Laser-based direct-write techniques for cell printing," *Biofabrication*, vol. 2, p. 032001, 2010.

[21] D. Eyers and K. Dotchev, "Technology review for mass customisation using rapid manufacturing," *Assembly Automation*, vol. 30, pp. 39-46, 2010.

[22] J. He, D. Li, B. Lu, Z. Wang, and T. Zhang, "Custom fabrication of a composite hemi-knee joint based on rapid prototyping," *Rapid prototyping journal*, vol. 12, pp. 198-205, 2006.

[23] S. Singare, L. Yaxiong, L. Dichen, L. Bingheng, H. Sanhu, and L. Gang, "Fabrication of customised maxillo-facial prosthesis using computer-aided design and rapid prototyping techniques," *Rapid Prototyping Journal*, vol. 12, pp. 206-213, 2006.

[24] C. Chang, M. Lee, and S. Wang, "Digital denture manufacturing-An integrated technologies of abrasive computer tomography, CNC machining and rapid prototyping," *The International Journal of Advanced Manufacturing Technology*, vol. 31, pp. 41-49, 2006.

[25] D. Eggbeer, R. Bibb, and R. Williams, "The computer-aided design and rapid prototyping fabrication of removable partial denture frameworks," *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, vol. 219, pp. 195-202, March 1, 2005 2005.

[26] A. Ovsianikov, B. Chichkov, O. Adunka, H. Pillsbury, A. Doraiswamy, and R. J. Narayan, "Rapid prototyping of ossicular replacement prostheses," *Applied Surface Science*, vol. 253, pp. 6603-6607, 5/30/ 2007.

[27] A. Jardini, M. Larosa, L. Bernades, C. Zavaglia, and R. Maciel Filho, "Application of direct metal laser sintering in titanium alloy for cranioplasty," in *6th Brazialian Conference on Manufacturing Engineering, pp1-3*, 2011.

[28] R. Bibb, D. Eggbeer, and R. Williams, "Rapid manufacture of removable partial denture frameworks," *Rapid Prototyping Journal*, vol. 12, pp. 95-99, 2006.

[29] B. Vandenbroucke and J.-P. Kruth, "Selective laser melting of biocompatible metals for rapid manufacturing of medical parts," *Rapid Prototyping Journal*, vol. 13, pp. 196-203, 2007.

[30] D. A. Hollander, M. von Walter, T. Wirtz, R. Sellei, B. Schmidt-Rohlfing, O. Paar, *et al.*, "Structural, mechanical and in vitro characterization of individually structured Ti–6Al–4V produced by direct laser forming," *Biomaterials*, vol. 27, pp. 955-963, 3// 2006.

[31] X. Li, J. Wang, L. L. Shaw, and T. B. Cameron, "Laser densification of extruded dental porcelain bodies in multi-material laser densification process," *Rapid Prototyping Journal*, vol. 11, pp. 52-58, 2005.

[32] R. Meszaros, R. Zhao, N. Travitzky, T. Fey, P. Greil, and L. Wondraczek, "Three-dimensional printing of a bioactive glass," *Glass Technology-European Journal of Glass Science and Technology Part A*, vol. 52, pp. 111-116, 2011.

[33] O. L. A. Harrysson, O. Cansizoglu, D. J. Marcellin-Little, D. R. Cormier, and H. A. West Ii, "Direct metal fabrication of titanium implants with tailored materials and mechanical properties using electron beam melting technology," *Materials Science and Engineering: C*, vol. 28, pp. 366-373, 4/1/ 2008.

[34] H. Cai, Z. Liu, K. Zhang, H. Leng, C. Sun, Z. Wang, *et al.*, "In vivo Study of a Self-Stabilizing Artificial Vertebral Body Fabricated by Electron Beam Melting," 2014.

[35] E. Vorndran, U. Klammert, A. Ewald, J. E. Barralet, and U. Gbureck, "Simultaneous Immobilization of Bioactives During 3D Powder Printing of Bioceramic Drug-Release Matrices," *Advanced Functional Materials*, vol. 20, pp. 1585-1591, 2010.

[36] L. Ciocca and R. Scotti, "CAD-CAM generated ear cast by means of a laser scanner and rapid prototyping machine," *The Journal of prosthetic dentistry*, vol. 92, pp. 591-595, 2004.

[37] S. V. Murphy and A. Atala, "3D bioprinting of tissues and organs," *Nature biotechnology*, 2014.

[38] X. Cui, K. Breitenkamp, M. Finn, M. Lotz, and D. D. D'Lima, "Direct human cartilage repair using three-dimensional bioprinting technology," *Tissue Engineering Part A*, vol. 18, pp. 1304-1312, 2012.

[39] B. Struecker, N. Raschzok, and I. M. Sauer, "Liver support strategies: cutting-edge technologies," *Nature Reviews Gastroenterology and Hepatology*, 2013.

[40] R. Chang, K. Emami, H. Wu, and W. Sun, "Biofabrication of a three-dimensional liver micro-organ as an in vitro drug metabolism model," *Biofabrication*, vol. 2, p. 045004, 2010.

[41] J. Snyder, Q. Hamid, C. Wang, R. Chang, K. Emami, H. Wu, *et al.*, "Bioprinting cell-laden matrigel for radioprotection study of liver by pro-drug conversion in a dual-tissue microfluidic chip," *Biofabrication*, vol. 3, p. 034112, 2011.

[42] K. Jakab, C. Norotte, B. Damon, F. Marga, A. Neagu, C. L. Besch-Williford, *et al.*, "Tissue engineering by self-assembly of cells printed into topologically defined structures," *Tissue Engineering Part A*, vol. 14, pp. 413-421, 2008.

[43] M. CSETE, B. SHEPHERD, S. DORFMAN, R. LAW, and C. KHATIWALA, "3D CELL BIOPRINTING FOR REGENERATIVE MEDICINE RESEARCH AND THERAPIES," *Gene Therapy and Regulation*, vol. 07, p. 1230004, 2012.

[44] L. Koch, S. Kuhn, H. Sorg, M. Gruene, S. Schlie, R. Gaebel, *et al.*, "Laser printing of skin cells and human stem cells," *Tissue Engineering Part C: Methods*, vol. 16, pp. 847-854, 2009.

[45] M. Gruene, A. Deiwick, L. Koch, S. Schlie, C. Unger, N. Hofmann, *et al.*, "Laser printing of stem

cells for biofabrication of scaffold-free autologous grafts," *Tissue Engineering Part C: Methods*, vol. 17, pp. 79-87, 2010.

[46] R. Gaebel, N. Ma, J. Liu, J. Guan, L. Koch, C. Klopsch, *et al.*, "Patterning human stem cells and endothelial cells with laser printing for cardiac regeneration," *Biomaterials*, vol. 32, pp. 9218-9230, 12// 2011.

[47] W. P. Syam, M. Mannan, and A. Al-Ahmari, "Rapid prototyping and rapid manufacturing in medicine and dentistry: This paper presents an overview of recent developments in the field of rapid prototyping and rapid manufacturing with special emphasis in medicine and dentistry," *Virtual and Physical Prototyping*, vol. 6, pp. 79-109, 2011.

[48] I. Ozbolat and Y. Yu, "Bioprinting towards organ fabrication: challenges and future trends," 2013.

[49] M. Al Mardini, C. Ercoli, and G. N. Graser, "A technique to produce a mirror-image wax pattern of an ear using rapid prototyping technology," *The Journal of prosthetic dentistry*, vol. 94, pp. 195-198, 2005.

[50] Q. Liu, M. C. Leu, and S. M. Schmitt, "Rapid prototyping in dentistry: technology and application," *The international journal of advanced manufacturing technology*, vol. 29, pp. 317-335, 2006.

[51] M. Wu, J. Tinschert, M. Augthun, I. Wagner, J. Schädlich-Stubenrauch, P. Sahm, *et al.*, "Application of laser measuring, numerical simulation and rapid prototyping to titanium dental castings," *Dental Materials*, vol. 17, pp. 102-108, 2001.

[52] K. F. Leong, C. K. Chua, W. S. Gui, and Verani, "Building Porous Biopolymeric Microstructures for Controlled Drug Delivery Devices Using Selective Laser Sintering," *The International Journal of Advanced Manufacturing Technology*, vol. 31, pp. 483-489, 2006/12/01 2006.

[53] K. Low, K. Leong, C. Chua, Z. Du, and C. Cheah, "Characterization of SLS parts for drug delivery devices," *Rapid Prototyping Journal*, vol. 7, pp. 262-268, 2001.

[54] M. Manzano and M. Vallet-Regí, "Revisiting bioceramics: Bone regenerative and local drug delivery systems," *Progress in Solid State Chemistry*, vol. 40, pp. 17-30, 8// 2012.

[55] C. Wu, Y. Luo, G. Cuniberti, Y. Xiao, and M. Gelinsky, "Three-dimensional printing of hierarchical and tough mesoporous bioactive glass scaffolds with a controllable pore architecture, excellent mechanical strength and mineralization ability," *Acta Biomaterialia*, vol. 7, pp. 2644-2650, 6// 2011.

[56] P. Sharp, C. Cooney, M. Kastner, J. Lees, R. Sasisekharan, M. Yaffe, *et al.*, "The third revolution: the convergence of the life sciences, physical sciences, and engineering," *Massachusetts Institute of Technology*, 2011.

[57] P. A. Sharp and R. Langer, "Promoting convergence in biomedical science," *Science*, vol. 333, p. 527, 2011.

[58] A. Bens, H. Seitz, G. Bermes, M. Emons, A. Pansky, B. Roitzheim, *et al.*, "Non-toxic flexible photopolymers for medical stereolithography technology," *Rapid Prototyping Journal*, vol. 13, pp. 38-47, 2007.

[59] D.-T. Chou, D. Wells, D. Hong, B. Lee, H. Kuhn, and P. N. Kumta, "Novel processing of Iron-Manganese alloy based biomaterials by inkjet 3D printing," *Acta biomaterialia*, 2013.

[60] A. A. Balandin, S. Ghosh, W. Z. Bao, I. Calizo, D. Teweldebrhan, F. Miao, *et al.*, "Superior thermal conductivity of single-layer graphene," *Nano Letters*, vol. 8, pp. 902-907, Mar 2008.

[61] C. Lee, X. D. Wei, J. W. Kysar, and J. Hone, "Measurement of the elastic properties and intrinsic strength of monolayer graphene," *Science*, vol. 321, pp. 385-388, Jul 2008.

[62] K. S. Novoselov, A. K. Geim, S. V. Morozov, D. Jiang, Y. Zhang, S. V. Dubonos, *et al.*, "Electric field effect in atomically thin carbon films," *Science*, vol. 306, pp. 666-669, Oct 2004.

[63] J. S. Bunch, S. S. Verbridge, J. S. Alden, A. M. van der Zande, J. M. Parpia, H. G. Craighead, *et al.*, "Impermeable atomic membranes from graphene sheets," *Nano Letters*, vol. 8, pp. 2458-2462, Aug 2008.

[64] F. J. Tölle, M. Fabritius, and R. Mülhaupt, "Emulsifier-Free Graphene Dispersions with High Graphene Content for Printed Electronics and Freestanding Graphene Films," *Advanced Functional Materials*, vol. 22, pp. 1136-1144, 2012.

[65] C. Ladd, J. H. So, J. Muth, and M. D. Dickey, "3D printing of free standing liquid metal microstructures," *Advanced Materials*, vol. 25, pp. 5081-5085, 2013.

[66] C. Chu, G. Graf, and D. W. Rosen, "Design for additive manufacturing of cellular structures," *Computer-Aided Design and Applications*, vol. 5, pp. 686-696, 2008.

[67] Stratasys. (2013, 11/16). *Stratasys Design Series*. Available: http://www.stratasys.com/3d-printers/design-series

[68] B. Mustaffa, H. Narahara, and H. Suzuki, "Electronic Circuit Fabrication Using Inkjet Printed Silver Nanoparticles For SFF," in *Proc. of Japan Society for Precision Engineering National Conference*, 2004, pp. 83-84.

[69] M. MOLITCH-HOU. (SEPTEMBER 6, 2013, 11/16). *3D Printing Breakthrough Yields Organic and Inorganic Multimaterial Vista Printhead*. Available: http://3dprintingindustry.com/2013/09/06/3d-printing-breakthrough-yields-organic-and-inorganic-multimaterial-vista-printhead/

[70] M. S. Mannoor, Z. Jiang, T. James, Y. L. Kong, K. A. Malatesta, W. O. Soboyejo, *et al.*, "3D Printed Bionic Ears," *Nano Letters*, vol. 13, pp. 2634-2639, 2013/06/12 2013.

[71] S. Khalil, J. Nam, and W. Sun, "Multi-nozzle deposition for construction of 3D biopolymer tissue scaffolds," *Rapid Prototyping Journal*, vol. 11, pp. 9-17, 2005.