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A Review on Additive Manufacturing for Bio-Implants

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***Abstract*—Bio materials are those materials that are accepted by living tissues and can be used for tissue replacements. Dental implants are the most improved treatment for teeth that have been either extracted or have been ejected as a result of periodontal disease that provides a living PDL connection for titanium implants. The bioimplant consists of a hydroxyapatite coated titanium screw, unsheathed in cell sheets made from immortalized human periodontal cells. 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 future. AM is a technique for creating complex geometries, not possible with traditional subtractive manufacturing, directly from computer designs through the sequential solidification of layers of material. The technology was originally limited to model making and prototyping applications due to insufficient mechanical properties and resolution. However, with advances in materials processing, the application of the technology has expanded into areas such as medical, aerospace and automotive.**

Keywords*—*Bio-Implants, Additive Manufcturing, AM Technology, Bioprinting, Nano Maerials & Implants.

I. INTRODUCTION

Bio materials are those materials that are accepted by living tissues and can be used for tissue replacements. On a macroscopic level these devices are used to fix or replace a bone and to support its healing process. With the worldwide increase in the average age of population there is a subsequent increase in the number of surgical procedures which has in turn urged researchers to improve and optimize bio materials. Although implant treatment has a high success rate, there are some fundamental vulnerability associated with osseointegration, the healing mechanism between the bone and the titanium implant fixture. The osseointegration process at the implant surface, however, does not incorporate the periodontal ligament (PDL) space. Additive Manufacturing is coming into its third decade of commercial technological development. During that period, we have experienced a number of significant changes that has led to improvements in accuracy, better mechanical properties, a broader range of applications and reductions in costs of machines and the parts made by them.

Worldwide, approximately 230 million major surgical procedures are performed on a daily basis. Most of these procedures involve reconstruction, repair, or replacement of one or more damage tissues or organs. Tissue engineering in combination with additive manufacturing has emerged as an alternative technique to regenerate damaged tissues and organs by developing patient-specific substitutes that restore, improve, or maintain tissue function. Engineering of functional tissues or organs requires a scaffold, which acts as a template for tissue regeneration. Additive manufacturing can help build such a template in a layer-by-layer fashion and is particularly appropriate for reconstructive surgery for facial trauma because scaffolds with patient-specific anatomical geometries can be fabricated. Currently, materials that facilitate bone ingrowth are widely used in reconstructive surgery for the treatment of trauma, but tissue engineering scaffolds will see more widespread clinical usage as research and clinical translation continues. One of the most common additive manufacturing technologies for tissue engineering scaffolds is material extrusion additive manufacturing, in which a variety of materials can be extruded including polymers, hydrogels, and ceramic pastes. For thermoplastics, the process is also known as fused deposition modelling (FDM). During material extrusion additive manufacturing, filaments are extruded from a nozzle and positioned relative to one another according to a pattern chosen by the user.

II. TECHNOLOGY FOR FABRICATION OF BIOIMPLANTS

Additive 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. 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. Other advantages include customization, lower cost,

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lesser tooling machines and little technical expertise required to operate machines. 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.

A. Bioprinting

One of the most sophisticated applications of additive biomanufacturing involves the fabrication of scaffolds. For the specific requirements of periodontal regeneration, multiphasic scaffolds have significant advantages as they facilitate compartmentalized tissue healing [7,8]. While the strategy appears promising, the approach needs to be optimized and tested into large animal studies and eventually in human clinical studies. By taking advantage of the power of additive (bio)manufacturing, exciting developments in the field of regenerative periodontology are envisioned. One such development involves bio fabrication technologies, such as bioprinting, which refers to printing of all of the components that form a specific tissue, including living cells embedded in matrix materials, to generate tissue analogue structures [9]. While applications of bioprinting of oral tissues are still in early stages, this strategy has displayed interesting results in various preclinical studies and seems encouraging, progressing beyond templates and models [10]. However, for successful clinical translation it is important to develop a road map, which includes studies to receive the required FDA approval and CE marking at an early stage in the process. In addition to these general approvals, there is an urgent need for guidelines and protocols for standardization in the field of additive biomanufacturing. Subsequently, these manufacturing and engineering standards need to be merged with biological considerations. Above all, it is important to take into account that bioprinting, seen from a translational research point of view, is primarily focused at patient-specific customization. Therefore, one of the biggest challenges will be establishing standardization, while still allowing for patient-specific adjustments.

B. Modern Manufacturing Technologies

In the current digital age of manufacturing, technologies such as computerized tomography scanners (CT scan for bone) and magnetic resonance imaging (MRI for soft tissue) scanners are used to examine and create a three-dimensional computer image of any damaged bone or soft tissue in the human body [11–13]. These images can be imported into computer aided design (CAD) software tools and create replicated modals of the damaged areas. This process gives way to the potential manufacturing and production of complex porous bio-scaffold structures with the help of additive rapid prototyping (RP) also known as three-dimensional printing or more general as additive manufacturing. There is a variety of additive rapid prototyping technologies which are generally referred to by the technique with which they form solid parts. All techniques share the same overall process shown below where the printing stage (building stage) is different. Note that the sub-process of conversion into machine language is made by saving the CAD file as a .STL file format (Stereolithography). The figure-1 below shows the processes which is followed for the additively manufacturing process.

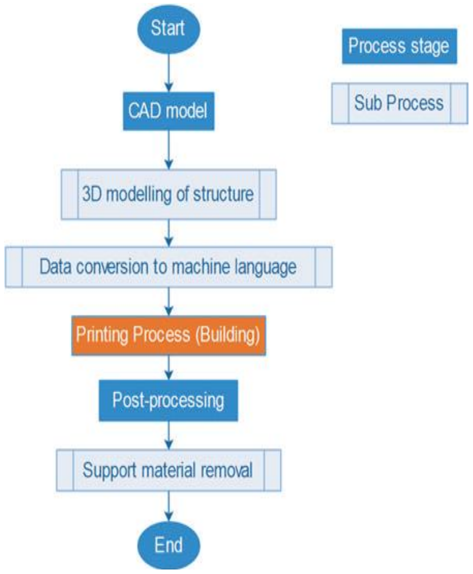

Figure 1: - Additive rapid prototyping process diagram

III. TYPES OF AM TECHNOLOGIES

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: (i) directly or (ii) indirectly.

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

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 microscale 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). 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.

A. Fused Deposition Modelling (FDM)

Layer by layer, a part’s cross-sectional geometry is laid out by extruding a build material in a filament form through a temperature-controlled nozzle. After the build material exits the nozzle, it hardens and binds to the layer below [14]. The materials used with this technology are mainly thermoplastics such as ABS, Polycarbonate, biodegradable PLA or PLGA [15] and also low melting point metals [16]. This technology is known for its rough surface finish, slow build speed and the minimum wall thickness is relatively large due to the nozzle

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diameter. In addition, a support material is required [14, 16] (Fig. 2).

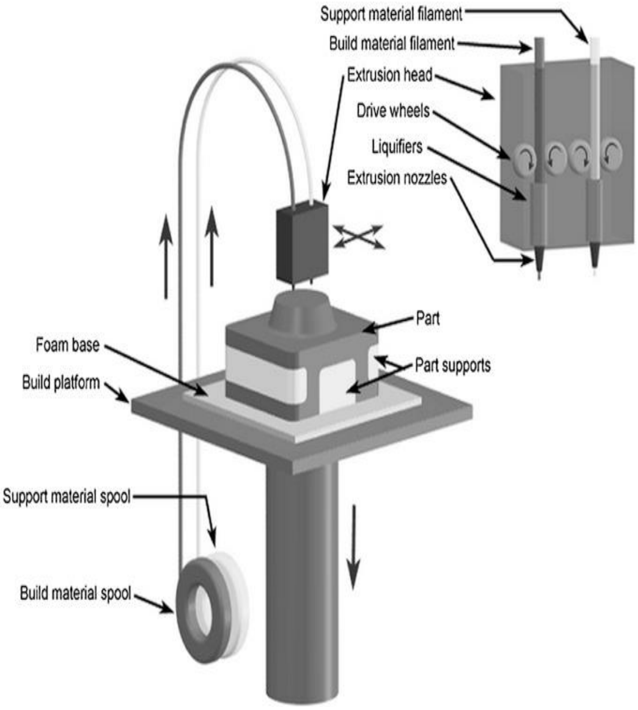

Figure 2: - Fused Deposition Modelling (FDM)

B. Three-Dimensional Printing (3DP)

Layer by layer a powder-based material is thinly laid out and an ink-jet printing head with a liquid adhesive binds the loose particles together [16] (Fig. 3). 3D printing build materials include polymers, ceramics, sand and metal powders such as stainless steel. This technology is well known for its fast process, rough surface finish, weak parts and producing models with multiple colours. No support material is required and a post-processing of hardening is necessary [14]. Biocompatible and biodegradable materials can be used in this technique although the selection process of finding the right binding adhesives is complex. Due to the powder grain size, binding material and post processing methods, 3DPs are restricted in the bio-molecule incorporation and the minimum building size [17].

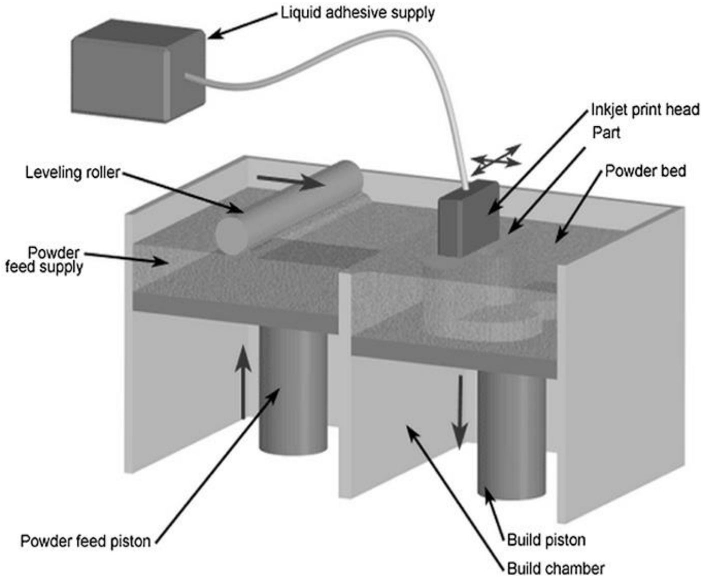

Figure 3: - Three-Dimensional Printing (3DP)

C. Stereolithography (STL or SLA)

A UV laser is focused at a vat of liquid photosensitive polymer which traces one cross section at a time. This technology is known for a smooth surface finish and highly detailed parts, average build speed and a wide range of materials. This requires a support structure, support removal process and post-curing [14, 16] (Fig. 4).

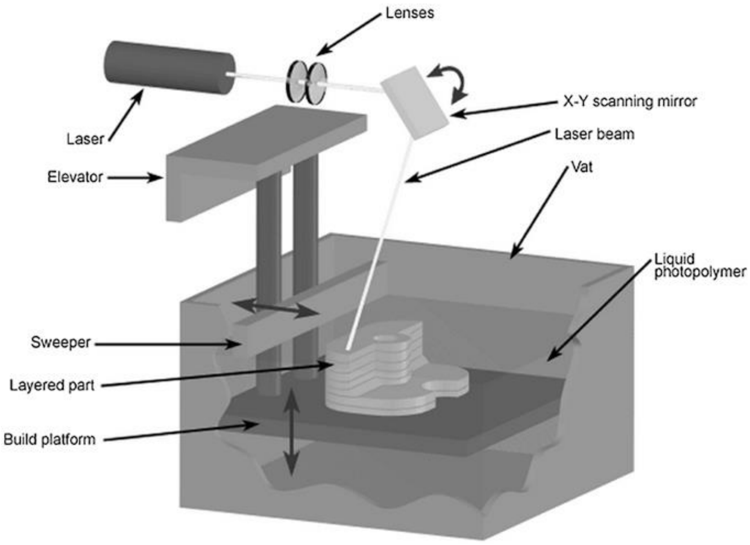

Figure 4: - Stereolithography (STL or SLA)

D. Selective Laser Sintering (SLS)

The SLS technology combines the selective laser technique of the SLA technology and the powder material layering from 3D printers. Together, this technology is known for average surface finish due the large powder particles [16], good part stability and functionality, fast building speed and a wide variety of materials such as rubber like materials (SOMOOS), biocompatible and biodegradable polymers and metal composites with high heat applications. No support material is required and only minimal post processing is necessary [14] (Fig. 5).

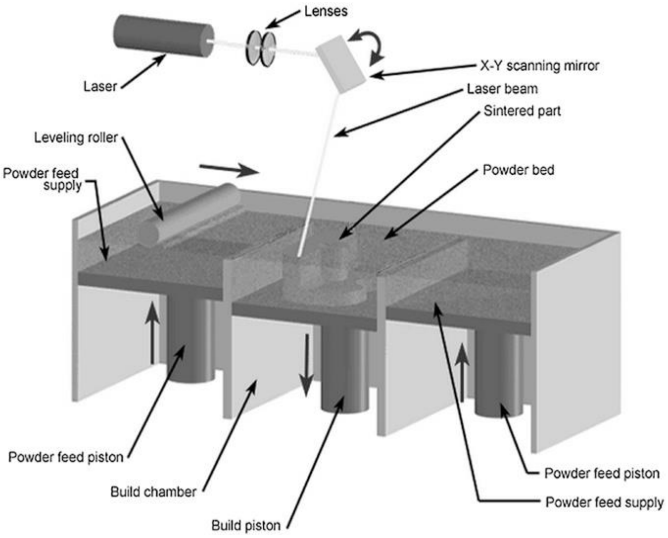

Figure 5: - Selective Laser Sintering (SLS)

IV. BIOIMPLANTS AND THEIR TYPES

Bioimplants possess individual specific requirement and are usually produced in low volume. As their name suggests, bioimplants are for medical-clinical applications such as porous implants, prosthetics, drug delivery and biosensors they can be described 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

- Biological implants
- Biologized implants
- Bio functional implants

The difference between the three classifications is mainly due to the number of cellular components that make up the implants.

A. Biological Implants

Biological implants are manufactured from biological materials such as cells, protein etc. using bioprinting. Usually two key components are needed for making biological implants; firstly, a bioprinter containing materials such as living cells (i.e. stem cells or tissue spheroids and biodegradable scaffolds/matrices (hydrogels) which predetermine the 3D form for creating the organ. 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. 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 bio fabrication techniques (iii) Characterization of the bio fabricated construct to focus on the issues of immunology, toxicity and ability to remain its form after post implantation. 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.

B. Biologized Implants

Biologized implants are made of a combination of cellular components and permanent biomaterials. The difference between biological implants and biologized implants are the degradability of the 3D structure. Biologized implants structures are permanent and nonbiodegradable. The permanent biomaterial structures are biocompatible and provide the mechanical stability for cellular colonization. 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, vinum and aluminum oxide ceramic. This section will focus on orthopedics and dental implants mainly made from metals and using indirect printing methods made of titanium and its alloys. Most dental implants and many other orthopedic implants are now made up 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. 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. A lot more in rapid prototyping for dental application can be further explored through additive manufacturing.

C. Bio Functional Implants

Biofunctionctionalised refer to the field of surface treatment with the purpose to optimally use the surface for life science applications. This means that after implantation, bioactive surfaces of Biofunctionctionalised implants interact with the biological environment in the body. The development and application of customized properties of the base materials required. The materials for biofunctionalized 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. 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®. Elke and team were able to print simultaneous geometry with hydroxypropyl methylcellulose (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.

D. Tissue Engineering & Regenerative Medicine

Tissue engineering (TE) is the application of principles and methods of engineering & life sciences to create living tissue to replace or repair skin of a failing organ or a damaged or missing body part [1]. The term tissue engineering was first presented to the broad scientific community in 1993 by Langer and Vacanti [2] for the development of biological substitutes that maintain, improve or restore tissue function.

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Tissue engineered products (TEPs) typically are a combination of three components, i.e. isolated cells, an extracellular Matrix (all cells surrounded by a complex mixture of non-living material) and signal molecules, such as growth factors. The term 'scaffold' provides new possibilities for the extracellular matrix by maintaining a three-dimensional space for the formation of new tissues with appropriate function. It is well known that the interaction of the cells and the extracellular matrix is of great importance for the intended function of the final product. Polymers having excellent physical properties such as high surface area, high porosity, interconnectivity pores of the nanofiber matrices with well-controlled degradation rates and biocompatibility of the base polymer make it an ideal candidate for developing scaffolds for tissue engineering [3].

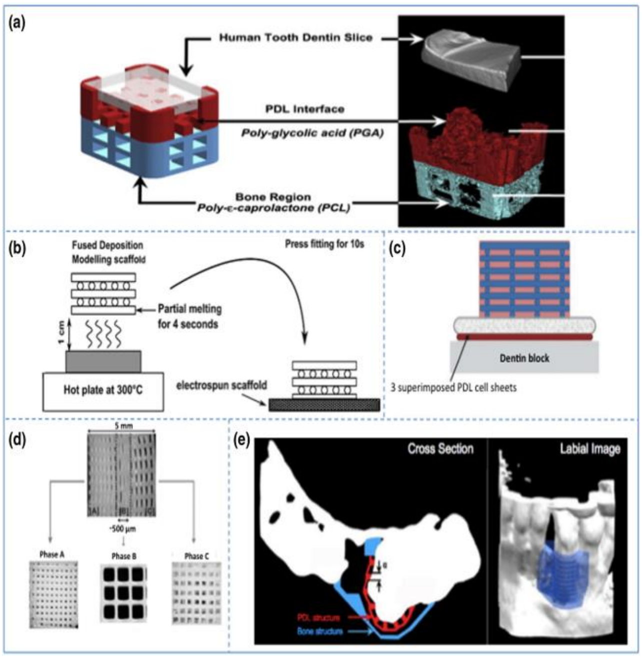

Figure 6: - Additively manufactured scaffolds for periodontal regeneration. (a) Biphasic scaffold facilitating fiber orientation (b) Biphasic scaffold in combination with cell sheet technology (c) Enhanced biphasic scaffold (d) Triphasic scaffold (e) First additively bio manufactured scaffold for periodontal regeneration applied in human

E. Nano Materials and Implants

There are entirely different physical and chemical properties of conventional macro-materials as compare to smaller nanosized particles specially phenomena such as the quantum size effect become more prominent when particulate matter decreases to 100 nm or smaller [4]. The basic concept of large surface area to volume ratios allows nanophase materials for more favorable interactions with surrounding structures. Several researches shown that nanocrystalline layer encourages the growth and bonding of the surrounding bony tissue. In vitro research has also shown that bone-forming cells (osteoblasts) adhere better and deposit more calcium on materials with a grain size in the nanometer range than on conventional materials with a grain size in the micrometer range [6]. Proper, coordinated function of both types of cells is essential for the formation and maintenance of healthy bony tissue and, therefore, for strong bonding between the implant and the surrounding bone [5]. This is extremely important for implants that are attached without the use of bone cement. Thin layer of nanocrystalline structure on artificial implants such as artificial hips, which are usually made of titanium or alloys of cobalt and chromium could help to reduce the problems of wear or implant loosening. This nanocrystalline structure is harder, smoother, good binder and consequently results in more resistance of wear of the artificial socket, which is generally made of a special type of polyethylene. Hydroxyapatite is a natural component of bone, 70% of which consists of the mineral hydroxyapatite, with the remaining 30% consisting of organic fibers (collagen). Coating of hydroxyapatite with a grain size in the nanometer, rather than the micrometer scale as earlier makes it more biocompatible and more like that of natural hydroxyapatite in bone which likewise has a nanocrystalline structure (grain size less than 50 nm). Nanoparticles of hydroxyapatite can also be used to repair the bony tissues of damaged bones which was first demonstrated in Maastricht University Hospital in 2000 to use an artificial hip with a hydroxyapatite nanocrystalline layer. Apart from hydroxyapatite, diamond and metal ceramic are other materials which are in use to make implants [6].

V. LIMITATIONS OF AM FOR MEDICAL APPLICATION

Although there is no doubt that medical models are useful aids to solving complex surgical problems, there are numerous deficiencies in existing AM technologies related to their use to generate medical models. Part of the reason for this is because AM equipment was originally designed to solve problems in the more widespread area of manufactured product development and not specifically to solve medical problems. Development of the technology has therefore focused on improvements to solve the problems of manufacturers rather than those of doctors and surgeons. However, recent and future improvements in AM technology may open the doors to a much wider range of applications in the medical industry. Key issues that may change these deficiencies in favor of using AM include:

– Speed
– Cost
– Accuracy
– Materials
– Ease of use

By analyzing these issues, we can determine which technologies may be most suitable for medical applications as well as how these technologies may develop in the future to better suit these applications.

VI. FURTHER DEVELOPMENT OF MEDICAL AM APPLICATIONS

It is difficult to say whether a particular AM technology is more or less suited to medical applications. This is because there are numerous ways in which these machines may be applied in this field. One can envisage that different technologies may find their way into different medical departments due the specific benefits they provide. However, the most common commercial machines certainly seem to be well suited to being used as communication aids between

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surgeons, technical staff and patients. Models can also be suitable for diagnostic aids and can assist in planning, the development of surgical procedures and for creating surgical tools and even the prosthetics themselves. Direct fabrication of implants and prosthetics is however limited to the direct metal AM technologies that can produce parts using FDA (The US Food and Drug Administration) certified materials plus the small number of technologies that are capable of non-load bearing polymer scaffolds. For more of these technologies to be properly accepted in the medical arena, a number of factors must be addressed by the industry:

– Approvals
– Insurance
– Engineering training
– Location of the technology

VII. CONCLUSION

In summary, additive manufacturing will enable the production or fabrication of improved medical implants. Additive manufacturing 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. 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.

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