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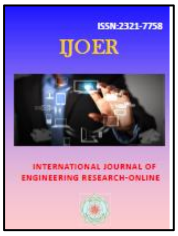
A REVIEW ON APPLICATION OF RAPID PROTOTYPING TECHNOLOGY IN BIOMEDICAL SECTOR

HETAL PUROHIT[1], J. J. DANGE[2]
[1]Student M.E, Department of Mechanical Engineering,
hetalswadia@gmail.com
[2]Professor, Department of Mechanical Engineering,
jayesh.dange111@gmail.com
[2]Lokmanya Tilak College of Engineering
Kopar Khairane, Sector 4, Vikas Nagar, Navi Mumbai, Maharashtra 400709, India



ABSTRACT

The layer by layer printing of three dimensional structures using a variety of engineering materials has made it possible to manufacture and develop any complex and customised products. This Rapid Prototyping technology (RPT) has its application not only in almost all engineering fields but also in biomedical applications such as development of functional implants, prosthesis, tissue engineering and surgical templates. This review emphasises on the significance of RP in biomedical sector. Bio-models are developed by acquiring patient specific data using imaging techniques, segmenting it and intern converting it into RP acceptable format. The compatibility of the process with a variety of bio-compatible materials has aided Bio-fabrication. However RPT has its own limitations when it comes to biomedical sector but with the rate of extensive research and developments, it can be predicted that RPT will evolve as a potential practical application.

Keywords: Rapid Prototyping, Biomaterials, Biocompatibility, Bioprinting

I. INTRODUCTION

Rapid Prototyping Technology (RPT), synonymous with Additive Manufacturing (AM) and 3D (Three Dimensional) Printing, is the latest buzzword in manufacturing sector. But this technology has been around since ages and was earlier known as Solid Freeform Fabrication (SFF). The (Building) construction industry has been utilising the basic principle of RPT since its inception. RPT was actually developed to produce functional prototypes quickly than making the prototypes in conventional ways, as this enabled companies to have better visualisation of a product before its full scale production thereby lowering product development time. Material addition layer by layer helped not only in reducing waste but also achieving profiles close to the designed profile and reduction in tooling requirement. This in turn led to saving the production cost. The technology which was used just for prototyping has gradually evolved into actual manufacturing technology. The technology has diversified into various forms which are now capable of utilising variety of raw materials ranging from polymers, ceramics and composites to metals, biomaterials and even building materials. RPT is best suited for applications involving customised, low volume production and complex structures.

The applications of RPT are widespread. Nannan GUO et al. have listed various sectors as aerospace, automotive, biomedical and energy where RPT has extensive use [9]. Parts manufactured for aerospace industry are mostly intricate and are made of advanced expensive materials in low volume. Apart from manufacturing, RP is not only also used for the repair of aircraft parts as compressor, turbine castings, combustor parts, housings and blades but Wind tunnel models of aircrafts, aerofoils and missiles can also be manufactured by utilizing this technology. In automotive sector, various structural and functional parts like gear box components, engine exhausts, camshaft covers, braking systems etc. are being manufactured by AM for luxury low volume cars, racing light-weighted cars and motorcycles. RPT can be used to develop prototypes for development and research purposes for fuel cells for improving energy efficiencies and power density which in turn, will help in reducing cost and development time.

Even Space instrumentation is not untouched by the benefits of RP. It has been used for prototyping, full mock ups to simplify the design of electrical harnesses or thermal insulation and testing articles like articles of lower interest and ground staff equipment. Apart from these, real flight structural and non-structural parts are also fabricated [16]. Textile industry, footwear design, furniture design, electrical appliances, architectural interior design, art and jewellery design are few other areas where RPT has been successfully deployed [13]. Biomedical applications have been dealt in detail in this paper.

II. RP IN BIOMEDICAL SECTOR

Medical science is very challenging and critical field. But with exponential growth in recent years, RPT offers promising solutions to these challenges. Medical models or bio-models or stereo models are the models developed using patient specific data [10]. They consist of 3D structures showing bone and vascular structures, foreign bodies, soft tissues or implants. J.J. Dange et al. have used 3D printing for extraction of knee joint parameters and in their analysis and have listed various steps used in the development of bio-model [11].

1. Getting CT/MRI scan data in the form of DIACOM files.
2. Developing the 3D BioCAD model
3. Converting the model into STL (Stereolithography) based model.
4. Evaluating the design.
5. Surgical planning and superimposition if desired.
6. Creation of RP model.
7. Validation of the model. [22]

In their paper, W.P. Syam et al. have enlisted how RPT is used in fabrication of biological prosthesis, implants, pre-surgical models and various scaffolds that can be used for cell growth [23]. In each case the primary data had been collected by Computed Tomography (CT) scans or Magnetic resonance imaging (MRI) scans. The two dimensional (2D) data thus obtained are processed by segmentation. During segmentation, soft tissues are separated from hard tissues. The 2D data received in DICOM (Digital Imaging and Communication in Medicine) file format is sliced using 3D slicer software [18]. Here the files are automatically layered. The region growing helps to split the scans and then the two dimensional CT scan contours are piled upon each other to make three dimensional (3D) images. In case of errors segmentation they can be manually corrected and further converted to STL (Stereolithography) format with software like ModelMaker, MIMICS, Analyse, Amira, 3D Doctor, Biobuild, Sliceomatic etc [22].

There are three types of rectifications that are mostly done on 3D surfaces. Duplicated verticals are unified by removing edges that are represented more than once. Duplicated faces are unified and isolated pieces are removed [18]. A.L. Jardini et al. in their work presented the use of RPT to produce patient specific and customised titanium implant for the reconstruction of the cranial defect surgically. Cranioplasty of a patient with a post trauma defect in right frontal bone was carried out. First the RP model was generated for planning of the surgery and understanding the fit of the actual implant and after making necessary corrections the actual implant was fabricated by metal laser sintering which had exact fit to the patient's skull. They also recognised the importance of good segmentation with good resolution and small pixel size for the final production of bio-model. This process usually requires the collaboration of engineers, radiologists and surgeons, since medical people have required hands on knowledge on segmentation [3]. This constitutes the evaluation of design and surgical planning phase. Conversion of 3D files to STL using biomedical software generates complex topography and the file size increases. So these files need to be worked on specific software for RP (Rapid Prototyping) like Magics, Geomagic. These software rectify any inconsistencies and optimize the triangular surface to have manageable file sizes, resulting in optimum construction time and material for bio-models thereby reducing the cost. If, the model is used for academic purposes it can be directly manufactured. But if, it is used for surgical planning which is usually the case, some alteration is required by the combined team of engineers and surgeons to create the final prototype. Then the model is produced using one of the many RP technologies and then it is validated for its suitability for the purpose.

III. BIOCOMPATIBILITY AND BIOCOMPATIBLE MATERIALS

Biomaterials are the materials that are used in medical devices, which are either in contact or are temporarily inserted or permanently implanted in the body and have very specific requirements [15]. The term *Biocompatiblity* means the ability of the material to co-exist with the living tissue without causing any immunological defects. A device might be made up of biocompatible materials but it still has to be tested for its biocompatibility. ISO 10993 has laid some specific recommendations about the biocompatibility of the medical devices and the materials used therein. The material should be "nontoxic, nonthrombogenic, noncarcinogenic, nonantigenic, and nonmutagenic" [15]. Biomaterials can be polymers, biodegradable and tissue-derived materials, bio-derived macromolecules, passive surface coatings, bioactive and tissue-adhesive materials, metals, ceramics, composites, and nano materials. Two primary categories of polymers that are used for 3D tissue/ organ printing are synthetic polymers and hydrogels. Commonly used synthetic polymers are polycaprolactone(PCL), poly(Lactic-co-Glycolide) (PGLA), polyethylene glycol (PEG) and Poloxamer 407. Other common polymers being polyamides (PA), polyvinylchlorides (PVC), polyethylene teraphthalate (PET-P), polymethyl methacrylate (PMMA), polytetrafluroethylene (PTFE), Poly(L-lactic acid) (PLLA), Polyanhydrides, Polyfumarates (PF), poly-etheretherketone (PEEK), Polyorthoesters [12,23]. These materials are mostly used because of their relative biocompatibility, tailorable properties and low cost. Some of the commonly used hydrogels are Alginate, Collagen, Gelatine, Fibrin and Hyaluronic acid (HA). Hydrogels scaffolds lack in mechanical properties. Chemical crosslinking in hydrogels improves the mechanical strength and stability of scaffolds thus produced [20].

Ceramics are widely used in dental and orthopaedic applications. Alumina, Zircon Dioxide, Carbons, Bio-glass, Titanium Oxide, Tri-calcium phosphate (TCP) and pyrolytic carbon are a few. Hydroxyapatite is another ceramic used generally in scaffold designs [7]. Scaffolds are very important in tissue engineering as they help in developing functional living implants obtained by cells from the cell culture and when developed with the help of fused deposition modelling technique, the scaffolds having properties close to natural bone and teeth can be developed [17].

Composites, as in any other application, are used for unique design requirements. Like cardio vascular catheters use coextruded tubes with wires in the wall and radio opaque fillers (barium sulphate) are used to increase the visibility during x-ray. Engineering plastic based newer carbon fibre is also being investigated for orthopaedic application [15]. Poly L-lactic acid (PLLA) and chitosan combined with hydoxyapatite microspheres have been used to replicate natural bone structure. Poly propylene fumarate (PPF) which is an unsaturated linear polymer combined with β-TCP forms a composite which has improved mechanical properties of material during early stages of degradation [4].

Metals are also considered suitable as biomaterials due to their high strength, corrosion resistance, ease of manufacturability and low cost. The metals are employed in most of the applications in orthopaedic and dental implants. Surgical grade stainless steel, mainly austenitic SS-316L, CoCrMo and pure titanium and its alloys (α, α+β and β alloys), most important being Ti_6Al_4V, are the most trusted for the purpose [3, 19]. Ti_6Al_4V is α+ β type alloy. Selective layer sintering (SLS) is employed for manufacturing the implants made out of titanium and its alloys. J. P. Kruth et al. have studied the feasibility of manufacturing medical parts with these biomaterials using SLS and found it to be fully suitable [5]. Tan et al. have studied the mechanical properties and biocompatibility of Ti_6Al_4V cellular scaffolds along with the manufacturing and topological design [24].

IV. BIOFABRICATION AND 3D BIOPRINTING

Bio-fabrication is a technology where in complex living biological products are produced from the inputs that are either biology based or inspired by biology. The inputs here can be living cells, molecules, extra cellular matrices (ECM) and engineered biomaterials. Biofabrication is the merger of cell &development biology, bio material science and mechanical engineering. Biofabrication encompasses tissue engineering also. Whereas tissue engineering is mostly related to repair, replacement and regeneration of diseased or injured human tissues and organs, Biofabrication has a broader scope. It has various technologies in its arsenal like solid scaffold based biofabrication, printing of organs, inkjet printing, biospraying and many others [21]. To overcome the shortcomings of traditional tissue engineering, the new innovative approach of "Biopatterning, 3D Bioprinting and Biofabrication" was suggested to form 2D and 3D constructs.

In 2010, an organisation called *International Society of Biofabrication* (ISBF) was formed. In the 4th annual conference of ISBF the former president, Sun W, proposed a 4-level classification of 3D bioprinting based on the materials used. In level-1, non-biocompatible materials are used to make medical models for academic purposes. In level-2, 3D printing of on-demand prosthesis with biocompatible materials is included. Level-3 and 4 are entirely related to tissue engineering and regenerative medicines. Level-3 covers printing 3D scaffolds using biodegradable materials and level-4 includes 3D printing of living cells and ECMs [14].

3D Bioprinting Techniques for tissue engineering are mostly modified forms of existing RP techniques using non-biomaterials. There are basically three major types of bioprinting techniques available: inkjet or droplet technique, extrusion or dispensing technique and laser-assisted technique [1]. Inkjet technique is similar to the existing inkjet printing on paper. It uses a bio-ink and a movable substrate. The ink droplets can be generated using either thermal or piezoelectric forces. Some printers also use pneumatic pressure assisted techniques which can open a microvalve under a particular constant pressure but here maintaining the droplet size and flow continuity is a challenge [8]. Extrusion technique is similar to standard Fused Deposition Modelling (FDM). The biomaterial, usually synthetic polymers and hydrogels, is extruded using mechanical or pneumatic dispensing system. Multiple heads can be used to print cells and tissues simultaneously. In laser assisted technique, there is a thin film coated with cells/ hydrogel called donor layer. The focused laser ray stimulates a small portion of the film allowing the film to absorb the laser and gets heated and generates a cell bubble which is propelled towards substrate [12]. It is an expensive and complex technique but has higher throughput, cell viability and resolution. Other than the major ones, there are processes like valve based printing, which controls the biomaterial droplet size by modulating pulses and spheroid printing [8].

V. CHALLENGES IN 3D BIO-PRINTING

RP was originally developed for a much widespread use in manufacturing sector and not specifically for the medical sector. Therefore certain challenges are yet to be met. First being the speed of the process. As the material deposition takes place layer by layer, which is fundamental technique of RP for the development of complex structures, the process becomes time consuming. A slight compromise between time and complexity is affordable in most manufacturing scenarios, but when it comes to tissue engineering this can have adverse effect on the viability of the cells [10]. Exposure to high temperature and pressure and the effect of environment for prolonged period can lead to the death of cells too. For implants and surgical planning time is crucial in case of emergencies. Second, the conversion of DIACOM files to STL is complicated and approximated, so sometimes minor mechanical and structural defects creep in during final stage. Third, there are some contradictory conditions where striking an optimum deal is time consuming and variable intensive, for proper cell ingrowth requirement of high porosity or larger pore size on the outer surface is there which contradicts with the requirement of mechanical properties [24]. For such applications algorithms are being researched to automate the design of such porous structures by controlling the variables for optimum results. Fourth, high production volume can't be achieved and commercialisation is not yet possible because the developments in the technology are still in their infancy. Fifth is the cost effectiveness and scalability in the 3D bioprinting.

Next is vascularisation which means formation of blood vessels. The tissues are complex structures with bold vessels embedded in them to carry nutrition to and waste from them. Developing a fully functional organ with full vascularisation is difficult. Scalability of bio-fabricated tissues is also an obstacle [21]. Advances and new researches are being made to overcome the problems in reaping benefits of 3D printing for biomedical sector completely. Using stem cells for Bioprinting can help in improving cell viability as human embryonic stem cells (hESCs) have the capability to self-renew it and have short cycle times and they can differentiate into any cell types. A. Faulkner Jones et al. have developed a valve based printer and conducted the first study on the response of hESCs to the Bio-printing. By varying cell concentration and culture time, they were able to create spheroid aggregates of homogenous size, viable and capable of differentiating. With the help of 3D printed hESCs, human tissue models can be developed which can be used for development of in vitro drugs and testing and organ regeneration [2].

VI. CONCLUSION

The capability of development of custom implants, prosthesis, surgical templates and tools, cells and tissues has enabled RPT to gain popularity in medical sector. It has been used successfully in many applications for surgical planning. There are numerous cases where the use of virtual and real RPT models has saved surgical time, blood loss and reduced risk and exposure to vital organs while surgeries. In case of implants and prosthesis generation, better fit and adaptation are achievable [6]. Tissue engineering is still catching up with the aid of RP but with the exponential rate of developments in Bio-fabrication and 3D Bio-printing and use of stem cells, printing of functional organs is not far-fetched. And thereby not only the problem of partial organ dysfunction can be resolved but also the gap between the demand and supply of the organs available for transplant could be reduced.

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