3D PRINTING TECNOLOGY IN MEDICINE - REVIEW


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This paper presents a review of 3D printing technology in medical application, materials used in 3D bioprinting, benefits, challenges as well as the future of additive manufacturing in medicine. This technology is going to revolutionize medicine, the flexibility of 3D printing allows designers to make changes easily without the need to set up additional equipment or tools. 3D bioprinting have a promising potential in organ transplantations and help to overcome in donor shortages issue. Printed highly accurate 3D model depending on the patient's MRI or CT scans, help the surgeons to planning before surgery and have more successful operations, as well as reduce time in the operating room

Keywords: 3D bioprinting, tissue engineering, organs printing, prosthetics

1. INTRODUCTION

1.1 General

3D printing or also known as *Additive manufacturing or layered manufacturing* are used to create a physical 3D object layer by layer from computer-aided-design (CAD) software. Due to numerous benefits of this technique such as quick production with any complex shape and enhancement of printing speed and precision, has been applied to and utilized by many different industries, including medical technology. The surgical planning, preparation of organ models, fast production of personalized scaffolds, and immediate printing at the defect site can be carried out by additive manufacturing technology based on a patient's imaging data such as X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans and ultrasounds (U.S. FDA, 2020), which is subsequently fed into the 3D printer (Pati et. al. 2016), printed model of congenital heart defects from CT scan data using two different 3D printing technics (*Fig. 1*).

Layered manufacturing brings new possibilities to the medical fields for building bionic organs or tissue and solving the problem of donor shortage (Kalaskar, 2017). In this regards, current paper shows the materials used in 3D printing technology in medical field, advantages, limitations, applications and the future of 3D printing technology in medicine.

1.2 3D bioprinting Materials

Generally, the 3D printed materials used in medicine must be printable, have adequate mechanical characteristics, biocompatible and biodegradable.

Bioactive and degradable materials used for drug delivery and tissue engineering applications such as ceramics, polymers and hydrogels. These materials should have the right chemical and physical qualities to support and maximize re-

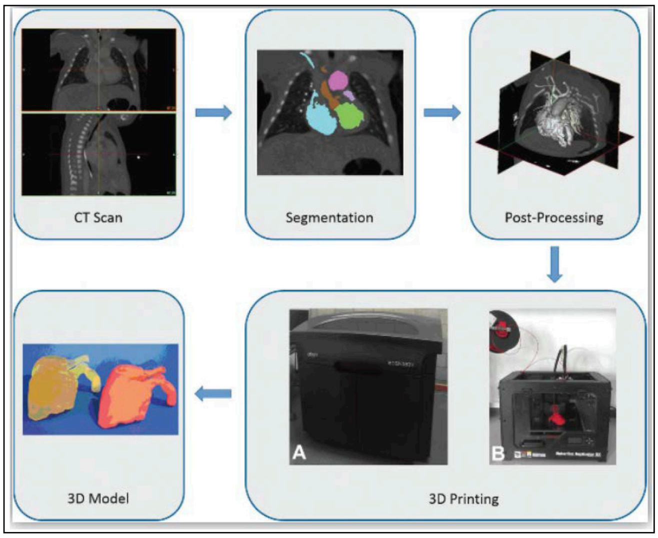

Fig. 1: 3D printed congenital heart defects model from CT scan data (Pati et. al. 2016)

generation, and it should degrade into harmless compounds that the host tissue can remove from the implantation site once the job is done (Jones, 2013; Mok et al., 2016).

Williams (2008), defines the biocompatibility as 'the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy'. For example, use non-degradable implants such as metals, polymers and ceramics for long term, they may corrode or wear, leading in the release of ions and wear debris, which may have undesired local or systemic consequences (Hallab et al., 2001; Gepreel and Niinomi, 2013). As a result, materials for long term use should be corrosion and wear resistant, emit little debris, and not cause the host system to react negatively.

2. ADVANTAGES

3D printing technology offers remarkable advantages for biomedical devices and tissue engineering due to its ability to produce low-volume parts that can be customized to meet the exact needs of patients. For instance, surgical implants are actually fabricated by casting in a mold for a desired part followed by chemical treatments for mechanical properties, required surface and aesthetic effects. These processes demand costly machinery, as well as the difficulty of titanium alloys crafting because of low elastic modulus, high mechanical strength and low thermal conductivity compared to steel make these material more expensive to manufacture a specific graft (Balazic et al., 2007). These operations can also produce a huge a mounts of material waste and energy intensive. 3D printing offers a new way to make a verity of practical biomedical products such as orthopedic grafts.

The advantages of using layered manufacturing technology over traditional manufacturing methods include its ability to provide designers with more freedom to create lightweight and customized implants and effectively solve the donor shortage problem for organ transplantations. Although 3D printing doesn't require specific tools or components, the cost per part remains constant. From minimally invasive surgery to cancer therapy, and from birth defect treatment to functional prostheses for amputees, all sectors of medicine and surgery are looking for advances enabled by 3D printing to improve human life quality or help patients live longer. Further development of human tissue and organs using this technology is still challenging due to its various limitations (Woodruff et al., 2012; Hutmacher et al., 2013).

3. LIMITATIONS

Despite the potential advantages of 3D printing in the medical product is still require extensive research and development to be truly effective. The lack of variety and diversity in 3D printable biomaterials is one of the major challenges. Although many printable materials have excellent properties for many other external applications, biocompatible implantable materials require specific properties that take into account both physiological conditions and interactions with the local body environment, making development much more difficult (Tasoglu and Demirci, 2013). For example, metal materials commonly used for permanent implants due to good mechanical properties, but the high elastic modulus of the metals might cause an elastic incompatible between the bone and the implant. Natural polymers such as sodium, collagen and alginate have a strong biocompatibility but low mechanical properties. Furthermore, there are no international standards for selecting medical materials for 3D printing; as a result, only synthetic evaluations based on function, structure, and clinical effects, rather than evaluations based on reliable indicators and sufficient experimental evidence.

Although cells can be directly printed at this stage, considerable work remains to be done in order to attain the aim of in vitro tissue engineering (Quan, 2015). Because the Extra Cellular Matrix (ECM) is a complex system with various components, it is challenging to reproduce its structure and biological activity in vitro. Current approaches, which predominantly stack cell-seeded hydrogels, are unable to address cellular nutrition and oxygen supply concerns. A significant number of cells cannot be provided for larger scaffolds at this time. Preprophase cells do not acquire an appropriate supply of nutrients as compared to cells that connect to the surface of scaffolds. That is, the cells persist in 3D space in a state of disequilibrium (Yan et al., 2010). For the continued development of printed scaffolds, tissues, and organs, further restrictions such as cell survival, development, differentiation, and fusion must be overcome.

4. 3D BIOPRINTING APPLICATIONS

Blood vessels, cells, cartilages, bandages, bones, maxillofacial implants and liver tissues for drug tests have all been successfully printed using 3D printing technology (Ozbolat and Yu, 2013; Ventola, 2014). In the following sub-sections will discuss the medical applications in tissues and organs printing, surgical planning, prosthetics and implants and medical training.

4.1 Tissues and organs printing

3D printing is already being utilized in studies to create tissue structures and human organ (Mannoor et al., 2013; Sawkins et al., 2015). 3D bioprinting can be combined with biocompatible microfluidics to produce highly complex structures that work similarly to natural human organs and able one to print living tissues with high speed and precision (Kolesky et al., 2014). This technology has the potential to transform medicine, printing organs directly in the body in the operating room, or printing organs that could be transferred to human donors. However, it's a challenging task to use biocompatible tissue constructs perfused with vascular network, also creates time constraints when printing living cells because to avoid cell damage due to the lack of oxygen.

One of the potential ways to print 3D cell structure is to add the cells in a scaffold. Scaffold is made out of biodegradable materials, due to facility of bio-printability and naivety of the structure, are widely used by researchers (Chua and Wai, 2015). However, it can be a challenge when use to construct small diameters blood vessels (Weinberg and Bell, 1986). (Kachouie et al., 2010) produced a new technique free from scaffold where cells encased in hydrogel were utilized to form tissue blocks that mimicked the target tissue or organ in specified geometric patterns.

Autologous grafts have traditionally been utilized to replace missing segments. These grafts are taken from another region of the patient's body, and this procedure has the potential to result in the loss of function at the donor site (Millesi, 2007). Functional nerve grafts for the treatment of peripheral nerve lesions were also produced using this technology, researchers were able to bio-print a nerve graft (Marga et al. 2012).

Faulkner et al. (2015) showed the ability of 3D bio-printing to print mini-livers using cultivated, patient-specific cells to introduce 3D objects that are function and viable for weeks after printing like a native liver. The goal of this research to develop personalized medicine and animal-free medication trials. While (Reiffel et al. 2013) showed the capability of the 3D printing technique to construct complicated geometries by printing a human-sized artificial ear.

4.2 Surgical planning

Surgical planning is one of the potential applications of 3D printing that has surfaced (*Fig. 2*). A highly trained and experienced surgeon who can make quick decisions during the operation is required for operational surgery on complex organs like the brain and heart, as well as anatomical specimens

Fig. 2: 3D printing- medical applications (a) 3D printed brain model (Ploch, et. al. 2016), (b) Patient holding her heart model used in planning for a double aortic arch surgery at Nicklaus Children's Hospital (Adams et. al., 2018)

like the pelvis and spinal cord. Surgeons can use 3D models to evaluate the damaged organs, explore various approaches, and gain hands-on experience. This approach dramatically reduces operation time and, as a result, improves the surgical outcome for patients, surgeons, and their care providers (Klein et al., 2013).

4.3 Prosthetics and implants

Recent advances in 3D printed affordable and patient custom-fit prosthetics help to improve people's life who suffered from hereditary deformity or accident (Elahinia et al., 2012) (*Fig. 3*). Within 24 hours, prosthetic limbs of any shape, size, or complexity can be created using a patient's CT or MRI pictures (Ventola, 2014).

Making customized dental implants was one of the first medical applications of 3D printing. Rapid prototypes, dental crowns and trial restorations are all regularly prepared using 3D printing technology (Eggbeer et al., 2005, Berman, 2012). The preparation of dental prosthesis can be greatly accelerated and improved with 3D printing. It was discovered that fabricating surgical guides enhanced the accuracy of dental implant placement (Liu et al., 2006).

Fig. 3: 3D printed titanium thumb prosthesis (Adams et. al., 2018)

Several cases of successful procedures using 3D printed polyetherketoneketone implants to replace parts of the skull have been described (Foletti et al., 2012). Printed cranial implants can be used to replace a patient's skull and can be designed to fit the defect properly using MRI or CT images. Plastic implants can also be manufactured more quickly than traditional titanium cranial implants. This is a significant factor since it allows patients to save time and reduces the risk of infection and brain damage.

4.4 Medical training

The use of cadaveric materials to train new medical doctors has been controversial. This is due to both ethical concerns and the high cost of the procedures. For many circumstances, including those in which using a cadaver is not an option, 3D printing technology may offer an innovative and successful substitute by replicating accurate complicated anatomical organs using high resolution MRI or CT scans. Furthermore, 3D printing's capacity to generate several replicas of any anatomical subject in various sizes provides a significant benefit in training facilities (Sheth et al., 2016).

5. 3D BIOPRINTING FUTURE

3D bioprinting of in vitro models is an exciting area of research that has yielded some promising preliminary results in recent years. The large range of 3D printing processes now accessible has enormous potential for facilitating the creation of realistic in vitro models. A comprehensive grasp of the principle, optimization, and standardization of the printing process with respect to the ultimate desired objective, as well as compliance with good manufacturing practice, are required for the effective application of 3D printed tissues as in vitro disease models. As a result, tactics aimed at understanding the various stages of disease progression and development within 3D printed tissue grafts are in high demand.

Using these revolutionary 3D printing technologies, the cost of drug screening on illness models can be significantly decreased by miniaturization while keeping its unique physiological features. The cost can be decreased even more by sharing digital data among users in research communities. 3D printed in vitro disease or tissue models, on the other hand, could be a potent substitute for in vivo animal models or even human clinical trials in drug development, cosmetics development, and toxicological testing, making it an attractive alternative for translational medical research.

Because of its adaptability, 3D printing may be used in a variety of nontraditional medical applications, including the construction of smart sensors for monitoring, precise bio-scaffolds, mechanobiology platforms, small implanted devices, and the integration of sensing and signaling. This, however, necessitates more research into a new class of printer-friendly biomaterials. Aside from novel materials, new hardware and software interfaces are needed to print varied materials at higher spatial resolutions than are now accessible (Kalaskar, 2017).

6. CONCLUSION

The development of 3D printing applications is a significant step forward in modern biomedicine. 3D printing's flexibility allows designers to make modifications quickly and simply without the need for extra equipment or instruments. These capabilities have inspired a surge in interest in medical 3D printing. There is no doubt that 3D printing, in general, may serve hugely persisting needs in today's healthcare systems, as it is projected to facilitate the supply of necessary devices and materials, making the entire manufacturing process less time and money consuming.

When choosing a material for medical applications, a variety of factors must be considered; not only must the material properties be adequate for the use, but the host tissue reaction after implantation must also be considered. In general, materials use in 3D bioprinting should be biocompatible, biodegradable and have good mechanical properties.

3D printing technology is going to transform medicine, whether it is patient specific surgical models, custom-made prosthetics, personalized on-demand medicines, or even 3D-printed human tissue. As its core 3D printing is the use of computer guidance technology to create 3D objects.

In the future, 3D bioprinting technology may be used to create therapeutically appropriate tissues and complex organs, which could change organ transplantation by addressing challenges such as donor scarcity, rejection and infection. In an ideal world, stem cells taken from a single patient might be developed into organ-specific cells and put into a bioprinting technology to create a personalized functional organ.

In medicine, 3D bioprinting still offers a lot of potential, and it will undoubtedly transform areas like tissue engineering, drug screening, and high-throughput biological testing. Despite its enormous potential for tissue regeneration and drug screening, this technology is still in its early stages and a lot of biological and engineering challenges still have to be addressed.

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8. REFERENCES

Adams, J., Alexander A., et. al. (2018), *"Medical Additive Manufacturing/3D Printing"*, Faculty of Medicine, Nursing & Health Sciences, Monash University, SME Medical AM3DP Workgroup, Annual report, 2018.

Balazic, M., Kopac, J., Jackson, M.J., Ahmed, W. (2007), *"Review: titanium and titanium alloy applications in medicine"*, Int J Nano Biomater 2007;1. http://dx.doi.org/10.1504/IJNBM.2007.016517.

Berman, B. (2012), *"3-D printing: the new industrial revolution*", Bus Horiz. 2012;55(2): pp. 155–62.

Chua, C.K., Wai, Y.Y. (2015), *"Bioprinting principles and applications"*, 1st ed. World Scientific Publishing Company; 2015. 296 p. Available from: https://books.google.com/books?id=nhK3CgAAQBAJ&pgis=1.

Eggbeer, D., Bibb, R., Williams, R. (2005), *"The computer-aided design and rapid prototyping fabrication of removable partial denture frameworks"*, Proc Inst Mech Eng., 2005;219(3): pp 195–202.

Elahinia, M.H., Hashemi, M., Tabesh, M. and Bhaduri, S.B. (2012), *"Manufacturing and processing of NiTi implants: a review"*, Progress in materials science, 57(5), pp. 911-946.

Faulkner, A., Fyfe, C., Cornelissen, D.J., Gardner, J., King, J., Courtney, A. and Shu, W., (2015), *"Bioprinting of human pluripotent stem cells and their directed differentiation into hepatocyte-like cells for the generation of mini-livers in 3D"*. Biofabrication, 7(4), p. 044102.

Foletti, J.M., Lari, N., Dumas, P., Compes, P., Guyot, L. (2012), *"PEEK customized implant for skull esthetic reconstruction"*. Rev Stomatol Chir Maxillofac, 2012;113(6):468–71.

Gepreel, MA-H., Niinomi, M. (2013), *"Biocompatibility of Ti-alloys for long-term implantation"*. J Mech Behav Biomed Mater 2013; 20:407–15.

Hallab, N., Merritt, K., Jacobs, J.J. (2001), *"Metal sensitivity in patients with orthopaedic implants"*. J Bone Joint Surg Am. 2001;83(3):428.

Hutmacher, D.W (2013), *"A road map for a tissue engineering concept for restoring structure and function after limb loss"*. J Mater Sci Mater Med 2013;24(11):2659–63.

Jones, J.R. (2013), *"Review of bioactive glass: from Hench to hybrids"*. Acta Biomater 2013;9(1):4457–86.

Kachouie, N.N., Du, Y., Bae, H. (2010), *"Khabiry M, Ahari AF, Zamanian B, et al. Directed assembly of cell-laden hydrogels for engineering functional tissues"*. Organogenesis 2010;6(4):234–44.

Kalaskar, D. (2017), *"3D Printing in Medicine"*, Elsevier, 1st Edition - April 1, 2017, p 219.

Klein, G.T., Lu, Y., Wang, M.Y. (2013), *"3D printing and neurosurgery – ready for prime time?"*. World Neurosurg, 2013;80(3–4):233–5

Kolesky, D.B., Truby, R.L., Gladman, A.S., Busbee, T.A., Homan, K.A., Lewis, J.A. (2014), *"3D bioprinting of vascularized, heterogeneous cell-laden tissue constructs"*. Adv Mater, 2014;26(19):3124–30

Liu, Q., Leu, M.C., Schmitt, S.M. (2006), *"Rapid prototyping in dentistry: technology and application"*. Int J Adv Manuf Technol, 2006;29(3–4):317–35.

Mannoor, M.S., Jiang, Z., James, T., Kong, Y.L., Malatesta, K.A., Soboyejo, W., et al. (2013), *"A 3D printed bionic ear"*. Nano Lett, 23;2013:2634–9.

Marga, F., Jakab, K., Khatiwala, C., Shepherd, B., Dorfman, S., Hubbard, B., et al (2012), *"Toward engineering functional organ modules by additive manufacturing"*. Biofabrication, 2012;4(2):022001.

Millesi, H. (2007), *"Bridging defects: autologous nerve grafts"*. Acta Neurochir Suppl, 2007; 100:37–8.

Mok, S-W., Nizak, R., Fu, S-C., Ho, K-WK., Qin, L., Saris, D.B., et al. (2016), *"From the printer: Potential of three-dimensional printing for orthopaedic applications"*. J Orthopaed Transl, 2016; 6:42–9.

Ozbolat, I.T., Yu, Y. (2013), *"Bioprinting toward organ fabrication: challenges and future trends"*. IEEE Trans Biomed Eng., 2013;60(3):691–9.

Ploch, C., Mansi, C., Jayamohan, J., and Kuhl, E. (2016), *„ Using 3D Printing to Create Personalized Brain Models for Neurosurgical Training and Preoperative Planning"*, World Neurosurgery, V (90), 2016, pp. 668-674. https://doi.org/10.1016/j.wneu.2016.02.081

Quan, W. (2015), *"3D-printed alginate/hydroxyapatite hydrogel in combination of Atsttrin to repair bone defects"*. [dissertation]. Hangzhou: Zhejiang University; 2015. Chinese.

Reiffel, A.J., Kafka, C., Hernandez, K.A., Popa, S., Perez, J.L., Zhou, S., et al (2013). *"High-fidelity tissue engineering of patient specific auricles for reconstruction of pediatric microtia and other auricular deformities"*. PLoS One. 2013;8(2).

Sawkins, M.J., Mistry, P., Brown, B.N., Shakesheff, K.M., Bonassar, L.J., Yang, J. (2015),*"Cell and protein compatible 3D bioprinting of mechanically strong constructs for bone repair"*. Biofabrication, 2015;7(3):035004.

Sheth, R., Balesh, E.R., Zhang, Y.S., Hirsch, J.A., Khademhosseini, A. and Oklu, R., (2016), *"Three-dimensional printing: an enabling technology for IR"*. Journal of Vascular and Interventional Radiology, 27(6), pp. 859-865.

Tasoglu, S., Demirci, U. (2013), *"Bioprinting for stem cell research"*. Trends Biotechnol 2013;31(1):10–19.

U.S. FDA, (2020), Food and Drug Administration, *"3D Printing of Medical Devices,"* last modified March 26, 2020, https://www.fda.gov/medicaldevices/products-and-medical-procedures/3d-printing-medical-devices

Ventola, C.L. (2014), *"Medical Applications for 3D Printing: Current and Projected Uses"*. P T, 2014;39(10):704–11.

Weinberg, C.B., Bell, E. (1986), *"A blood vessel model constructed from collagen and cultured vascular cells"*. Science. 1986;231(4736):397–400

Williams, D.F. (2008), *"On the mechanisms of biocompatibility"*. Biomaterials 2008;29(20):2941–53

Woodruff, M.A., Lange, C., Reichert, J., Berner, A., Chen, F., Fratzl, P., et al. (2012), *" Bone tissue engineering: from bench to bedside"*. Mater Today 2012;15(10):430–5.

Yan, Y., Li, S., Xiong, Z., Wang, X.H., Zhang, T., Zhang, R.J. (2010), *"Fabrication technology of tissue engineering scaffold based on rapid prototyping"*. J Mech Eng 2010;46(5):93–8

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