Review Article

A Review on Organ Printing: Computer Aided Tissue Engineering

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ABSTRACT

Organ Printing is an application of stereolithography first introduced by Chuck Hull in 1984 and has gained momentum since. Also called as Bioprinting, it involves 3D printing of organs using different Biofluids and cell assembly techniques. The main purpose is to overcome the receding number of donors of organs due to many factors. Therefore, Bioprinting offers a better approach for solving modern crisis. It not just helps in upgradation of Organ transplant techniques, but also propels studies and researches, thus, playing its better part in health ecosystem. Bioprinting works in a synchronous manner with the existing medical hardware. Through communication, the bioprinting software intercepts a draft for the specimen and then transfers the necessary to the printing apparatus. The bio-inks and hydrogel then, form the synthetic organ as per the design received, the usage of bio inks, self-assembling cells, and hydrogels which are led to produce the synthetic organ with the ability to retain all the physiological functions as the natural organ. Bioprinting offers many advantages compared to the traditional 2D tissue engineering. It's more accurate, produces better results and, the end organs are more comparable to the actual one. Bioprinting was introduced in 1987 and since then it had seen many progressions and advancements, still the struggle to commercialize it and reduce the operational costs is continued. Bioprinting is not fully automated and needs human intervention and has room for errors, availability of a singular apparatus is also needed and, sourcing of materials is another challenge. Altogether, Bioprinting is an excellent craft of developing synthetic organs for medical uses and studies and it is still is not ripe enough to be capable of full-fledged functioning. Couple of decades would see the immense scaleup of this technique into a fully functioning sector of the health care system.

Keywords: Organ printing, bio-printing, 3D -inks, organ transplants, synthetic organs.

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INTRODUCTION

Organ Printing was introduced and rooted back in 1987 and is associated with study of cell coalescence and tissue assembly. Several topics that form the basis of this study comprise cell and tissue coalescence, fluidity of tissue, studies on embryonic tissue, tissue affinity, and more. Organ printing which is also defined as additive layer bilayer deposition of cell-matrix, is an emerging technique that is probable and promises superior techniques compared to the conventional solid scaffold-based tissue engineering. It is now considered a type of applied biology. The ultimate goal of 3D organ printing is to forge 3D vascularized organs that are fit for clinical implantation. Organ printing resembles the assembly of a blood vessel, without the support of any synthetic polymer and ensures that our technique is pro-biological and not an antagonist. Organ printing was influenced by the advancement in the demands for implants and severely low numbers of donors leading to progressive work towards tissue engineering. The existing technology doesn't permit swift modelling of new organs or tissue, focus has shifted towards using viscoelastic embryonic tissues with well-described flow behaviour. [1]

Organ transplant shortage faced by people emphasizes the existing slits in the current healthcare system. Many patients succumb to unavailability of compatible organs required for transplants. In 2015, more than 126,000 transplants were performed worldwide, an increase of almost 5.8% from the previous year. In spite of the surge in the number of transplants performed, the number of recipients transcend the number of donors and created distress. To receive a transplant there is a lot of waiting only for the compatibility to be approved before procedure, furthermore for the rest of their lives the recipients need to be on immunosuppressants. Initially, 2D cell culturing was introduced but was declared a failure to produce the desired products as the stem cells used would grow into diverse tissues and could not mimic the 3D cell engineering. Another factor is time. Not all people have this luxury and the recipients have to wait until the correct match due to lesser donors. Thus, the requirement of acute methodologies to emerge is much awaited.[2]

3D organ printing is a revolutionary technology that can make medical care faster, effective, and more personalized. This technique enables researchers to develop well-defined 3D scaffolds seeded with cells in a rapid, inexpensive, and high throughput manner. Bio printing of organs and tissue patches from one's own cells can reduce the chance of rejection and eliminate the need for organ donors. Organ printing is analogous to the first printing press by Johannes Gutenberg. Printing requires 5 basic components for its operation: a written text, ink, paper, movable parts and a printing press. Similarly, the organ printing technology requires the draft of the organ, a dispenser, a biomaterial cartridge, biomimetic hydrogel and the bio-ink of self-assembling cells. All components are individually under development but the main hurdle here is putting them in synchrony to produce a satisfactory outcome.[3]

Organ printing as a concept was formalized in the year 1993 by Langer and Vicanti where the scaffolds were described in detail. Chuck Hull invented stereolithography in 1984. It was the first utilization of the concept of 3D printing as research poured in a private company that went by the name of STRATASYS. They commercialized the first 3D printing in 1990 and renamed it as Fused Deposition Modelling (FDM). Soon after in 1993, Langer and Vicanti developed an idea for printing human organs used in transplants. In 1999, a 3D bladder with bio-ink was printed and cells were grown which then was quickly followed by development of the first functional animal kidney at Wake Forest Institute, US. There were significant improvements in the printing technology. RepRap developed a printer capable of self-replication. Soon after, ORGANOVO announced printing of the first ever human blood vessel in 2010 and next in 2014 a Norwegian woman made the first 3D printed skull.[4] Currently organ printing is still in its evolving and its influence is yet to be determined.

Methodology

3D bioprinting is a technique that 3D prints living skin, organs, and tissues from a patient's cell. 3D printing has been around for a while now, but it has recently gained the ability to create three-dimensional objects with the most minuscule of detail. After years of research and experimentation it became possible for us to bio print real human skin in the year 2013.

At TEDMED 2015, Anthony Atala from Wake Forest Institute gave an extended talk on what his team has gotten up to over the years with their ground-breaking tissue engineering techniques.[5] The field of regenerative medicine is concerned with the fabrication of replacement organs, tissues and other body parts to treat or even cure human disease.

Numerous milestones have been met in order to bring organ to life while back in year 2002, though the progress has been sluggard, it was seen in the year 2010 that is when the first blood vessel was printed. [6]

Zhengchu Tan, a researcher at Imperial College London's Department of Mechanical Engineering, explained about the challenges faced by the scientists. [6]

In order to 3D print a complete organ, it is necessary that all the different cells found must be implanted from stem cells. These cells then create a complex biological structure of the organ including proper arrangements of blood vessels which is then followed by testing and analysing the organ's ability to function properly in the body.

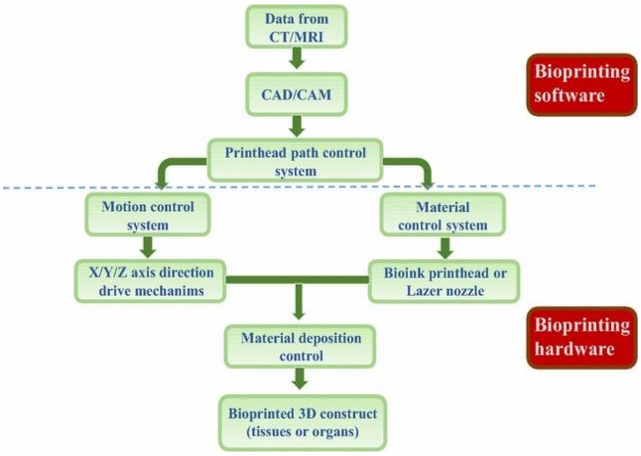

Figure 1: Differentiation between bioprinting software and bioprinting hardware.

The idea behind 3D bioprinting is to replicate the natural ability of cells to create new structures as they need them. Their consists of vast variety in technology of 3D bioprinting, therefore the selection of biomaterials is mostly related with the application of end product.

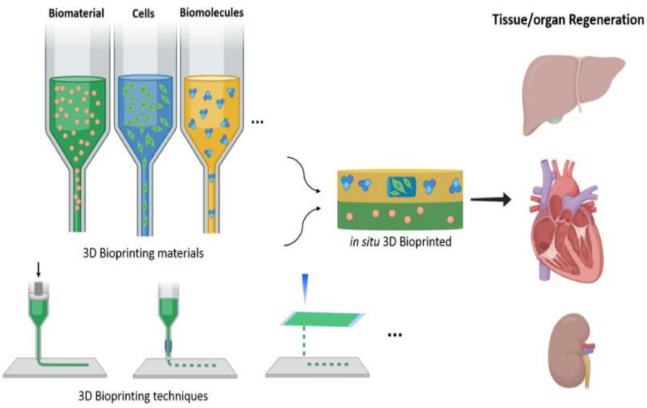

Figure 2: State-of-art of 3D bioprinting technology.

The Wake Forest Institute for Regenerative Medicine has already developed stem cell therapies for patients with spinal cord injuries, and other scientists are now trying to use the same technology to regrow insulin-producing cells that could be transplanted into diabetics. [6]

Using stem cell to create organs is a part of an emerging field called regenerative medicine that hold great promise for treating many of the 21st century's most critical health problems.

Scientists of United Therapeutics (Maryland, biotech company) have been working on a printer that would help to recreate the intricate details that would make up the lung along with all 23 branches accompanying by alveoli and capillaries.[7]

Bioprinting is a technology used in biomedical research and medicine to make a 3D biological structure from cells that are seeded onto a surface. The finished product can be used for various things like studying or treating conditions, or even making prosthetics. It all depends on what printer we choose to make and which method is being preferred. Following are the three most flexible methods -

1. Extrusion-based bioprinting
2. Droplet-based bioprinting
3. Digital light processing bioprinting

1. Extrusion based bio printing

It is one of the rapid prototypes, also called as 'Direct ink writing' or 'Solid freedom fabrication'.

Extrusion-based bioprinting has the potential to transform additive manufacturing, which has been limited to creating small-scale, customized products.

The tissue engineering approach can generate larger structures with many types of cells because they can be injected in droplets, which are then drawn together into a solid structure. Previous research was limited to creating no more than approximately 1mm in size.

Researchers have developed a new technique, could build structures up to three times larger than existing methods. This is accomplished by applying heat to produce tissue scaffolding that solidifies into place after cells are added, which ensures that the stem cell grow together in a uniform and functional way.

Extrusion-based bioprinting is one of the most preferred techniques due to its ability to create tissue structures with its adequate properties. Based on different modes this method is further classified into pneumatic-driven, piston-driven and screw-driven. [8]

It is a method of printing three-dimensional printing biologic matter.

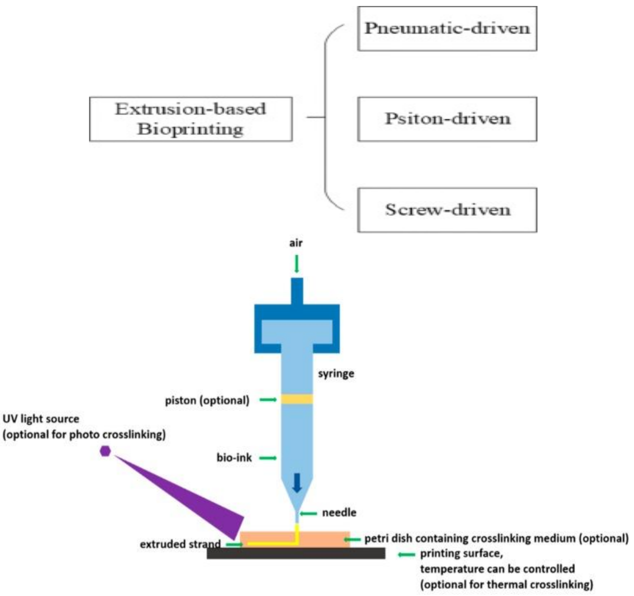

Figure 3, 4: Diagrammatic explanation of extrusion-based bioprinting.

2. Droplet based bio printing

Droplet-based bioprinting, also written as (DBB). This is a method used in bioprinting. The idea of bioprinting is to replicate natural ability of cell. The DBB bioprinting system can deposit precision-sized droplets to generate cell-laden, dense, and homogeneous 3D tissue structures. It has been shown that this technology is capable of printing multiple cell types at specific location with various particle sizes ranging from microns to nanometres.[9] The process starts with removing cells from an individual and mixing them with a special solution that encourages the cells to grow and proliferate.

The following are some application areas of DBB technology:

- Indoor location and tracking
- Augmented reality
- Gesture recognition
- Vehicle collision avoidance
- Robotics control
- Remote sensing
- 3D printing

This method is adaptive to engineer advanced tissues and organs. This technology is based on a novel printing platform that can generate 3D structures by printing multiple layers of materials with different viscoelastic properties.[10] The platform uses a programmable material dispenser to deposit materials with specific viscoelastic properties in a layered manner. This enables the generation of 3D architectures with high precision and control. The technology has been demonstrated to generate anatomically accurate 3D tissues, including liver and kidney tissues.

This viscoelasticity if a material determines how it will deform in a response to stress. Viscous materials deform slowly and tend to resist flow, while elastic materials deform quickly and return to their original shape when the stress is removed.

Many biological tissues, including liver and kidney tissues, have viscoelastic properties that can vary depending on the tissue location. For example, the viscoelasticity of liver tissue near the edge if the liver is different from that of liver tissue in the centre of the liver. This variability is important for proper organ function. The platform developed by researchers uses programmable material dispenser to deposit materials with specific viscoelastic properties in a layered manner. This enables the generation of 3D architectures with high precision and control. The technology has been demonstrated to generate anatomically accurate 3D tissues.

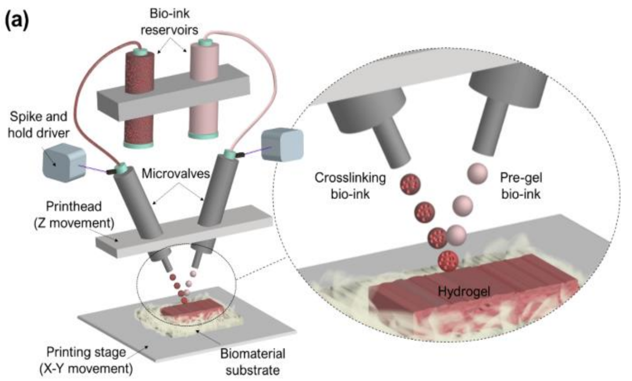

Figure 5: Diagrammatic explanation of droplet-based bioprinting.

3. Digital light processing bio printing

Digital light processing bioprinting (DLPBP) is a projection-based 3D printing methods which can print with higher resolution, finer structures and better mimic tissues. This is done by using a digital light processing system to project a UV image of the desired 3D object onto a photosensitive resin tray. The UV light hardens the resin in the desired areas, and the tray is then lowered slightly and the process is repeated. This is repeated until the entire 3D object has been created.[11]The stereo lithography apparatus (SLA) was invented by Chuck Hull of 3D Systems Inc. in 1986. The SLA works by projecting UV light from a vat of photopolymer resin onto a cross-section of the part being printed. The UV light cures the resin to a solid form. This resin is then reduced by its thickness followed by cross-section. The procedure is repeated until the organ or part is completely prepared.

The projection head is equipped with a rotating platform that can be programmed to print in any direction, including up and down. This allows the printer to create objects with overhangs and undercuts.

3D printing is an additive process of making three-dimensional objects from a digital model by laying down successive thin layers of materials. 3D printing is used in many industries such as automotive, aerospace, dental, medical and construction.

One of the common types of printers is Fused Deposition Modelling (FDM) printer. FDM printer work on heating a thermoplastic filament and extruding it layer onto a build platform.[12] The filament is usually heated to a temperature above its glass transition temperature, so that it can be followed easily. As the filament is extruded, the printer head moves in the X and Y directions to create the required shape. The thickness of the layer may vary based upon the part of organ.

FDM printers are relatively low-cost and easy to use, making them popular for home and office use. They are also capable of printing a wide range of materials, including thermoplastics, metals and composites. However, FDM printers have some limitations, including a lack of detail in the printed parts and a tendency to wrap the part if the print is not properly supported.

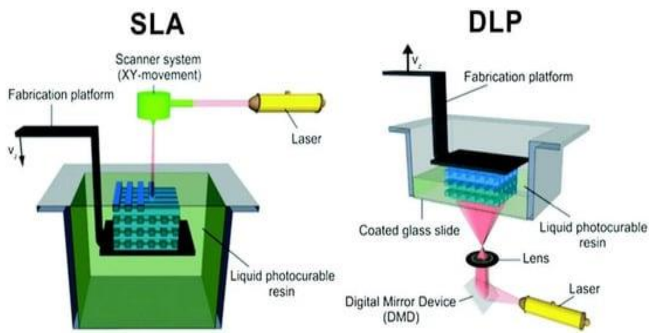

Figure 6: Differentiation between SLA and DLP

3D bioprinting, also known as "Additive manufacturing", is becoming popular with manufacturers.

It consists of many revolutionary benefits. Unlike other technologies it has its own drawbacks which has to be bought into consideration.

Advantages of Organ Printing

Out of all the trailblazing technologies, 3D bioprinting can be an intriguing one and with proper research can be a breakthrough technology in the field of medicine.

Given below are some of the pros of this technology which in the coming years can have a massive impact.

- Replacing organ donors- 3D organ printing would enable the patients receive an organ in a matter of days, instead of relying on organ donors.
- Creating a microenvironment-Apart from creating an artificial organ, bio printing can be used to make membranes and biological latex/ bio tapes. These can be used to create a microenvironment and mimic human body in vivo.[13]
- Minimal organ rejection- The rate of rejection will not be much since in bioprinting cultured cells or tissue is taken. This would ensure that there is no rejection of the organ post-surgery.
- Tissue repair-3D bioprinting is not restricted to creating a specific organ. This technology is also applicable for tissue repair and grafting.
- Teaching- Another tremendous use of this technology can be providing organs and tissues to doctors or medical students to practice the surgical procedures and also for them to have a better understanding.
- Research- Research is another area where bioprinting is a utility. Scientists or pharmacists can study about various diseases and their pathogenicity or the effect of drugs on the organs, this would reduce the need to sacrifice animals or perform human or animal trials.

Disadvantages of Organ Printing

Organ printing technology is still at its early stages of development and the possible disadvantages from the patient's point of view has to be studied. Some of the downsides of this technology includes:

- Lack of accessibility – Just like other technologies, 3D printing needs suitable technology and instruments to print an organ, which cannot be attained easily.
- Affordability- organ printing may not be the most economical technology for most people.
- The major challenge in organ printing is development of complete organs is laborious and the development of complex organs such has heart, liver, pancreas, etc. is still under process.[14]
- Authorized and proficient workers and highly qualified establishments are a necessity and yet to be set up.
- The process takes time which a lot of recipients do not have.
- Ethical and moral concerns.

CONCLUSION

Upcoming decades promise for wider usage of this technology, provided if we work on it. The shortage of organ donors leads to the introduction of this technique. More than 126,000 transplants performed faced the unavailability of donors. Many factors like ethical beliefs, traditions were also a hindrance. To counteract the inconsistent supply of organs 2D cell assembly techniques were introduced and failed due to inaccuracy in developing the desired end transplants. Another reason 3D bioprinting thrived is due to its efficiency. Bio-printing, apart from organ development has many potencies like creating microenvironments, repairing damaged tissues, research purposes, drug testing etc. The ripe nature of this technology has inhibited its acute usage and due to its uneconomical nature, hindrance in its application is evident. Organ printing has the scope of entering the core of medical field by reducing the shortage of organ donors and thereby improving patient compliance and thus providing them a new era of life.

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