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POTENTIAL OF 3D BIOPRINTING ORGANS/TISSUES

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Introduction

3D Bioprinting is the use of biochemicals, biomaterials, and living cells in the production of bioengineered structures (tissues and organs) with the assistance of computer-aided designs and additive construction. Bioprinting comes under the umbrella of Regenerative Medicine '(a field which focuses on regenerating human cells, tissues and organs to restore or establish normal function).

Objective:

This paper details the process of bioprinting, examines its applications, and assesses the scope of bioprinted organs and tissues.

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Need for Bioprinting

Bioprinting produces artificial organs or tissues that have the complete function of and are structurally similar to actual human organs. Thus, they can be used in various fields, specifically (1) as alternatives to real human organs and (2) in lab simulations for testing drugs and cosmetics.

1. **Use in Organ Transplant:** Each organ in the human body has a unique and exclusive function. When an organ significant to the body's function becomes defective, doctors try to address it via medicines and treatments such as dialysis for kidneys. However, over a period of time, the patient is left with no choice but to seek an organ transplant to overcome this constant hassle and suffering. Conventional organ transplants are medical procedures wherein a functioning human organ is extracted from a donor and implanted into the patient, replacing the patient's previous malfunctioning organ with a healthier one. However, conventional organ transplants have a limitation as there is a lack of organ donors while the waitlist for transplants grows every day. For example, in the US *'a new person is added to the transplant wait list every 9 minutes'**[1]. As a result, *'17 people die every day waiting for an organ transplant in the US.'**[2], as per the Health Resources & Services Administration. A similar issue plagues India, where the *'average wait time for a kidney transplant is between 3 to 5 years'**[3].

2. A potential alternative to these conventional transplants could be the implantation of bio-printed organs. These organs are artificially lab-created and specifically customised to the needs of each patient. If Bioprinted organs were to become popular, they would allow for more individuals to undergo transplants in a more timely manner, as the average printing process takes only 4-6 weeks.
Moreover, another problem with normal transplants is the recipient's possible rejection of the donated organ and the eventual immune attack launched against this organ. To avoid this outcome, patients often take immunosuppressant drugs; however, this compromises their immune system, which leaves them vulnerable to a vast host of diseases. This problem can be evaded with the use of 3D-printed organs made from the patient's

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cells. The bioprinted organ is recognised by the immune system as native to the patient's body, therefore, circumventing the issue of organ rejection. Additionally, if the donor is alive, the organ may develop health complications post-surgery or need the organ later in life, especially as life expectancy is constantly increasing due to new medical advances.

2. Performing safety tests on products using bioprinted organs: Another promising application of bioprinted organs and tissues in the testing of new drugs. Currently, developing drugs is slow, costly, and tedious. The current process of developing and delivering these drugs spans decades, costs billions of dollars, and is unsuccessful 95% of the time*4. Traditional drug development tests the impact of potential drugs on 2D lab-grown cells and in laboratory animal models. 3D bioprinted tissues grown from real human living cells mimic natural tissues way more closely, and thus testing on them is way more effective and cost-friendly. Similar to the testing of drugs on 3D bioprinted tissues is the testing of cosmetics on 3D bioprinted skin.

Process of production

A variety of different methods are used in 3d Bioprinting; thus, a generalised version of a common method used is detailed below.

Pre-printing: The first step of Bioprinting, known as pre-printing, consists of acquiring a scan of a sample organ using an imaging device such as a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). These scans are then converted into 3D models and altered to suit the patient's needs using specialised Computer-Aided Design (CAD) software. The model acts as the guide for the construction of the final scaffold or the highly porous architecture of the organ.

Preparation of bioink: Following this, a biopsy is conducted through which a sample of the patient's cells is extracted and cultivated within a hospitable environment, such as a bioreactor. The extracted cells are often a mix of specialised adult cells typical of the organ and pluripotent stem cells. Within the bioreactor, the cell mass is fostered under optimal conditions and fed with media or nutrients such as oxygen to keep them viable.

Once the cells are cultivated to an appropriate level, the creation of bioink (the printing fluid) commences. Bioink is composed of mostly hydrogels (hydrophilic polymers that retain large amounts of water while maintaining their original structure), various living cells, and biochemicals required for the nutrition and the upkeep of the cell's extracellular matrix. The reason water and biochemicals, such as oxygen, are essential to the ink is also to help in the proliferation and differentiation of cells. The specifics of each bioink differ according to the organ to be printed and the

Printing: This cell-laden bioink is then inserted into the cartridge of a specialised bioprinter. Depending on the complexity of the structure being printed, a variety of bioinks may be inserted into multiple printer heads. While there are various techniques of bioprinting and multiple types of bioprinters, generally, the printer additively (layer-by-layer) deposits the bioink to create the finalised structure following the architecture of the 3D CAD model.

Post-Printing: Before the printed organ or tissue is implanted, it undergoes post-printing, in which the structure is stimulated physically and chemically, necessary for the proper stabilisation and for providing signals to the cells to maintain their growth and normal function.

Case Studies:

Case study 1: Transplantation of bioprinted external ear, 3D Bio Therapeutics, USA, June 2022

3DBio Therapeutics assisted in the treatment of a patient suffering from microtia, a rare congenital birth defect in which one or both external ears are misshapen or incompletely formed. The traditional treatment for microtia involves taking cartilage from the patient's ribs, an invasive and inefficient procedure, or using porous

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Polyethylene (PPE) implants to form the replacement for the abnormal external ear. In this case, the company took a sample of the cartilage cells present in her misshapen right ear and grew them in an incubator. These living cells were then mixed with the company's collagen-based bioink. This mixture was inserted into a 3d printer to create a mirror replica of the patient's left healthy ear. A surgeon implanted the 3D-bioprinted construct under the skin of her right ear. The procedure was successful, and as a follow-up, the company is currently testing the treatment on 11 more patients currently enrolled in clinical trials.
'*Microtia affects around affects 1 in every 8000-10000 children in the US*'*[4]. This treatment highlights the potential of bioprinted organs in becoming the default solution to solving specific niche diseases. Despite the significance of this transplant, it should be noted that the external ear is a relatively easy tissue to construct due to the absence of blood vessels.

Case study 2: *Transplantation of Bioprinted bladder, Dr. Anthony Atala, USA, 2004*
Dr Anthony Atala, at the Boston Children's Hospital, surgically implanted a 3D bioprinted organ into a patient to replace his original defective bladder. The patient had spina bifida, a birth defect wherein the baby's spinal cord fails to develop properly. As a result, the patient's bladder became defective, which ultimately led to his kidneys failing, ruling out the possibility of dialysis. Thus, Atala turned to 3D bioprinting. He conducted a biopsy of the patient's kidney cells and cultivated them. He ultimately used these in his bioink to print a kidney scaffold from a modified inkjet printer. This scaffold was fostered in optimal conditions for two months and then implanted into the patient. The surgery was successful, with the patient mentioning, "It was pretty much like getting a bladder transplant, but from my own cells, so you don't have to deal with rejection". The bladder is still functional to date.

Case study 3: *Bioprinting of human skin for product testing, Dr. Sourabh Ghosh, IIT Delhi, India*
Professors at IIT Delhi led by Dr. Sourabh Ghosh have produced an accurate model of skin using a form of bioprinting. The skin mimics human skin in composition (the cells and extracellular matrix) and its structure (including the inner dermis, outer epidermis, and the undulatory junctions that holds the layers together). Unlike traditional tissue-engineered skin equivalents, the team's bioprinted skin had undulations. To create the model, the team designed the scaffold using a 3D CAD. The printing process then began with printing ten layers of the dermis using a bioink containing fibroblasts and eight layers of epidermis using a bioink containing keratinocytes and melanocytes. In addition, the team used a criss-cross printing pattern to ensure that the collage, which normally shrinks, doesn't shrink.
This project was funded by ITC Ltd., a company that produces cosmetic products. ITC Ltd. has since used the skin to test some of its products, a proof of concept that illustrates a practical use of the skin in countries such as India, where testing cosmetics on animals is prohibited. In collaboration with ITC Dr. Ghosh has also since developed the design of 3D-printed hair follicles, which will be printed onto their skin to provide a more accurate model of human skin.

Present status and future scope for commercialisation

The first bioprinted structure was produced in 1988, making bioprinting a relatively recent invention. Despite its recency, the field has made huge advances in a short amount of time and is bound to improve in technology and technique far more as time passes. It holds great promise for use in the field of medicine, especially in organ transplants.
Experts believe that eventually, bioprinted organs will be a viable alternative to transplants – reducing the waiting time and rejection chances and customising organs as per the precise need of each patient. The question

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is not if but more when. When will the technology required to construct complex organs be developed? **Fabien Guillemot,** CEO of bioprinting company Poietits, states, "*We anticipate that clinicians will use in routine bioprinting and bioprinted tissue products made of the patient's cells.*" *[6] However, Guillemot expresses uncertainty as to when we will have the technology to make more complex organs stating, "*it's difficult to define when the world will be able to print organs"*.

On the other hand, Dickerson, from Bioprinting company nScrypt, estimates the timeline for the commercialisation of complex bioriented organs to be "around 4 to 8 years" *[7]. **Jennifer Lewis**, Head of Harvard University's Wyss Institute for Biologically Inspired Engineering, predicts that it would take around a "decade plus" *[8].

Bioprinted Tissues and models of organs are already being developed at a commercial scale. Companies such as Organovo are manufacturing bioprinted skin and liver models to be used for testing cosmetics and potential drugs.

As seen in case study 3, there is a potential for bioprinted skin to be used in the testing of cosmetics and skincare items. Similarly, other bioprinted tissues and organs, such as livers, can be used for testing the impacts of drugs on the human body. These 3D human tissues have the potential to accelerate the drug discovery process, enabling treatments to be developed faster and at lower cost," Keith Murphy, Organovo's CEO.

There are several countries, such as the US, that don't have any jurisdiction regarding the testing of cosmetics on animals. With bioprinted skin becoming a popular alternative in the future, the process of banning the cruel and unethical testing of cosmetics on animals could be catalysed.

In 2021 Bioprinting was valued at 1.7 billion USD. This is projected to increase at a compound annual growth rate (CAGR) of 15.8% and is conservatively projected to be worth 8 billion USD by the end of 2030 *[5]. This fact showcases the immense potential of growth bioprinting has and how much of an impact it will have on several industries in the future.

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Links:
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